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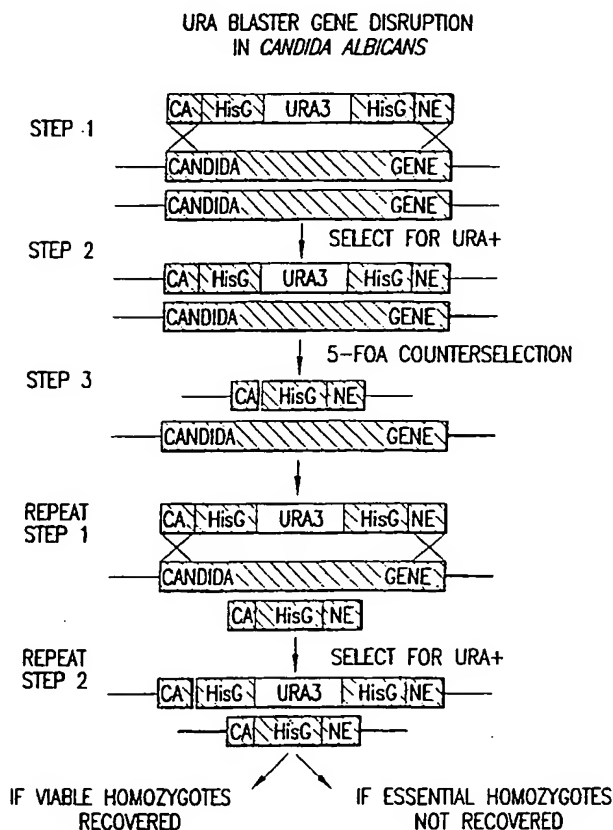
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(54) Title: GENE DISRUPTION METHODOLOGIES FOR DRUG TARGET DISCOVERY



(57) Abstract: The present invention provides methods and compositions that enable the experimental determination as to whether any gene in the genome of a diploid pathogenic organism is essential, and whether it is required for virulence or pathogenicity. The methods involve the construction of genetic mutants in which one allele of a specific gene is inactivated while the other allele of the gene is placed under conditional expression. The identification of essential genes and those genes critical to the development of virulent infections, provides a basis for the development of screens for new drugs against such pathogenic organisms. The present invention further provides *Candida albicans* genes that are demonstrated to be essential and are potential targets for drug screening. The nucleotide sequence of the target genes can be used for various drug discovery purposes, such as expression of the recombinant protein, hybridization assay and construction of nucleic acid arrays. The uses of proteins encoded by the essential genes, and genetically engineered cells comprising modified alleles of essential genes in various screening methods are also encompassed by the invention.

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GENE DISRUPTION METHODOLOGIES FOR DRUG TARGET DISCOVERY

5 This application claims priority to the United States provisional application serial no. 60/183,534, filed February 18, 2000, which is incorporated herein by reference in its entirety.

1. INTRODUCTION

10 The present invention is directed toward (1) methods for constructing strains useful for identification and validation of gene products as effective targets for therapeutic intervention, (2) methods for identifying and validating gene products as effective targets for therapeutic intervention, (3) a collection of identified essential genes, and (4) screening methods and assay procedures for the discovery of new drugs.

2. BACKGROUND OF THE INVENTION

15 Validation of a cellular target for drug screening purposes generally involves an experimental demonstration that inactivation of that gene product leaves the cell inviable. Accordingly, a drug active against the same essential gene product expressed, for example,
20 by a pathogenic fungus, would be predicted to be an effective therapeutic agent. Similarly, a gene product required for fungal pathogenicity and virulence is also expected to provide a suitable target for drug screening programs. Target validation in this instance is based upon a demonstration that inactivation of the gene encoding the virulence factor creates a fungal strain that is shown to be either less pathogenic or, ideally, avirulent, in animal model
25 studies. Identification and validation of drug targets are critical issues for detection and discovery of new drugs because these targets form the basis for high throughput screens within the pharmaceutical industry.

 Target discovery has traditionally been a costly, time-consuming process, in which newly-identified genes and gene products have been individually analyzed as
30 potentially-suitable drug targets. DNA sequence analysis of entire genomes has markedly accelerated the gene discovery process. Consequently, new methods and tools are required to analyze this information, first to identify all of the genes of the organism, and then, to discern which genes encode products that will be suitable targets for the discovery of effective, non-toxic drugs. Gene discovery through sequence analysis alone does not
35 validate either known or novel genes as drug targets. Elucidation of the function of a gene from the underlying and a determination of whether or not that gene is essential still present

substantial obstacles to the identification of appropriate drug targets. These obstacles are especially pronounced in diploid organisms.

C. albicans is a major fungal pathogen of humans. An absence of identified specific, sensitive, and unique drug targets in this organism has hampered the development of effective, non-toxic compounds for clinical use. The recent completion of the DNA sequence analysis of the entire *C. albicans* genome has rejuvenated efforts to identify new antifungal drug targets. Nevertheless, two primary obstacles to the exploitation of this information for the development of useful drug targets remain: the paucity of suitable markers for genetic manipulations in *C. albicans* and the inherent difficulty in establishing, in this diploid organism, whether a specific gene encodes an essential product. Co-pending provisional patent application, filed February 18, 2000, discloses the identification of dominant selectable markers, and the construction of two genes encoding those markers, which are suitable for transformation and gene disruption in *C. albicans*.

Current methods for gene disruption in *C. albicans* (Fig.1) typically involve a multistep process employing a "URA blaster" gene cassette which is recombined into the genome, displacing the target gene of interest. The URA blaster cassette comprises the *CaURA3* marker which is selectable in the corresponding auxotrophic host and which is flanked by direct repeats of the *Salmonella typhimurium* HisG gene. The URA blaster cassette also carries flanking sequences corresponding to the gene to be replaced, which facilitate precise replacement of that gene by homologous recombination. Putative heterozygous transformants, which have had one allele of the target gene deleted, are selected as uracil prototrophs, and their identity and chromosomal structure confirmed by Southern blot and PCR analyses. Isolates within which intrachromosomal recombination events have occurred between HisG repeats, leading to excision of the *CaURA3* gene and loss of the integrated cassette, are selected on 5-fluoroorotic acid (5-FOA) containing media. This allows a repetition of the entire process, including reuse of the Ura-blaster cassette, for disruption of the second allele of the target gene. In those instances in which the target gene is nonessential, homozygous gene disruptions are produced in the second round gene replacement and identified by Southern blot and PCR analyses.

However, homozygous deletion strains, which lack both alleles of a gene that is essential will not be viable. Accordingly, the Ura blaster method will not provide an unequivocal result, establishing the essential nature of the target gene since alternative explanations, including poor growth of a viable mutant strain, may be equally likely for the negative results obtained. More recent approaches for identification of essential genes, including those disclosed by Wilson, R.B., Davis, D., Mitchell, A.P. (1999) *J. Bacteriol.*

181:1868-74, employ multiple auxotrophic markers and a PCR-based gene disruption strategy. Although such methods effectively overcome the need to use the Ura Blaster cassette, determination of whether a given gene is essential, and therefore, a potentially useful target, remains labor-intensive and unsuitable for genome-wide analyses. Substantial effort is required to support a statistically valid conclusion that a given gene is essential when using either the Ura blaster cassette or multiple auxotrophic marker-based methods for gene disruption in *Candida albicans*. Typically, between 30 and 40 second round transformants must all be confirmed as reconstructed heterozygous strains (using PCR or Southern blot analysis) resulting from homologous recombination between the disruption fragment and previously constructed disruption allele, before statistical support to the claim that the gene is essential can be made. Moreover, since secondary mutations may be selected in either the transformation step or 5-FOA counterselection (if the Ura blaster cassette is reused), two independently constructed heterozygous strains are preferably examined during the attempted disruption of the second allele. In addition, demonstration that a particular phenotype is linked to the homozygous mutation of the target gene (and not a secondary mutation) requires complementation of the defect by transforming a wild type copy of the gene back into the disruption strain.

Finally, the Ura blaster method precludes direct demonstration of gene essentiality. Therefore, one is unable to critically evaluate the terminal phenotype characteristic of essential target genes. Consequently, establishing whether inactivation of a validated drug target gene results in cell death (i.e., a cidal terminal phenotype) versus growth inhibition (i.e., a static terminal phenotype) is not possible with current approaches, despite the value such information would provide in prioritizing drug targets for suitability in drug development.

Clearly, since current gene disruption methods are labor intensive and largely refractile to a high throughput strategy for target validation, there is a need for effective methods and tools for unambiguous, rapid, and accurate identification of essential genes in diploid, pathogenic fungi, and particularly, in *Candida albicans*. The present invention overcomes these limitations in current drug discovery approaches by enabling high throughput strategies that provide rapid identification, validation, and prioritization of drug targets, and consequently, accelerate drug screening.

3. SUMMARY OF THE INVENTION

The present invention provides effective and efficient methods that enable, for each gene in the genome of an organism, the experimental determination as to whether that gene is essential, and for a pathogenic organism, in addition, whether it is required for virulence or pathogenicity. The identification and validation of essential genes and those genes critical to the development of virulent infections, provides a basis for the development of high-throughput screens for new drugs against the pathogenic organism.

The present invention can be practiced with any organism independent of ploidy, and in particular, pathogenic fungi. Preferably, the pathogenic fungi are diploid pathogenic fungi, including but not limited to *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans* and the like.

In one embodiment, the present invention is directed toward a method for constructing a diploid fungal strain in which one allele of a gene is modified by insertion of or replacement by a cassette comprising an expressible dominant selectable marker. This cassette is introduced into the chromosome by recombination, thereby providing a heterozygous strain in which the first allele of the gene is inactivated.

The other allele of the gene is modified by the introduction, by recombination, of a promoter replacement fragment comprising a heterologous promoter, such that the expression of the second allele of the gene is regulated by the heterologous promoter. Expression from the heterologous promoter can be regulated by the presence of a transactivator protein comprising a DNA-binding domain and transcription-activation domain. The DNA-binding domain of this transactivator protein recognizes and binds to a sequence in the heterologous promoter and increases transcription of that promoter. The transactivator protein can be produced in the cell by expressing a nucleotide sequence encoding the protein.

This method for the construction of a diploid fungus having both alleles of a gene modified, is carried out, in parallel, with each and every gene of the organism, thereby allowing the assembly a collection of diploid fungal cells each of which comprises the modified alleles of a gene. This collection, therefore, comprises modified alleles of substantially all of the genes of the diploid organism. As used herein, the term "substantially all" includes at least 60%, 70%, 80%, 90%, 95% or 99% of the total. Preferably, every gene in the genome of the diploid organism is represented in the collection.

The present invention also encompasses diploid organisms, such as diploid pathogenic fungal strains, comprising modified alleles of a gene, where the first allele of a

gene is inactivated by insertion of or replacement by a nucleotide sequence encoding an expressible dominant selectable marker; and where the second allele of the gene has also been modified so that expression of the second allele is regulated by a heterologous promoter. In one aspect of the present invention, the alleles modified in the mutant diploid pathogenic fungal strain correspond to an essential gene, which is required for growth, viability and survival of the strain. In another aspect of the present invention, the modified alleles correspond to a gene required for the virulence and pathogenicity of the diploid pathogenic fungal strain against a host organism. In both cases, the essential gene and the virulence/pathogenicity gene are potential drug targets.

Accordingly, the present invention encompasses collections of mutant diploid fungal strains wherein each collection comprises a plurality of strains, each strain containing the modified alleles of a different gene. The collections of strains of the invention include modified alleles for substantially all the different essential genes in the genome of a fungus or substantially all the different virulence genes in the genome of a pathogenic fungus.

In another embodiment, the present invention is also directed to nucleic acid microarrays which comprise a plurality of defined nucleotide sequences disposed at identifiable positions in an array on a substrate. The defined nucleotide sequences can comprise oligonucleotides complementary to, and capable of hybridizing with, the nucleotide sequences of the essential genes of the diploid pathogenic organism that are required for the growth and survival of the diploid pathogenic organism, the nucleotide sequences of genes contributing to the pathogenicity or virulence of the organism, and/or the unique molecular tags employed to mark each of the mutant strains.

The present invention is also directed to methods for the identification of genes essential to the survival of a diploid organism, and of genes that contribute to the virulence and/or pathogenicity of the diploid pathogenic organism. First, the invention provides mutants of diploid organisms, such as mutant fungal cells, having one allele of a gene inactivated by insertion of or replacement with a disruption cassette, and the other allele modified by a nucleic acid molecule comprising a heterologous regulated promoter, such that expression of that second allele is under the control of the heterologous promoter. Second, such mutant cells are cultured under conditions where the second allele of the modified gene is substantially not expressed. The viability or pathogenicity of the cells are then determined. The resulting loss of viability or exhibition of a severe growth defect indicates that the gene that is modified in the mutant cells is essential to the survival of a pathogenic fungus. Similarly, the resulting loss of virulence and/or pathogenicity of the

mutant cells indicates that the gene that is modified contributes to the virulence and/or pathogenicity of the pathogenic fungus.

In yet another embodiment of the present invention, the mutant pathogenic fungal strains constructed according to the methods disclosed are used for the detection of antifungal agents effective against pathogenic fungi. Mutant cells of the invention are cultured under differential growth conditions in the presence or absence of a test compound. The growth rates are then compared to indicate whether or not the compound is active against a target gene product. The second allele of the target gene may be substantially underexpressed to provide cells with enhanced sensitivity to compounds active against the gene product expressed by the modified allele. Alternatively, the second allele may be substantially overexpressed to provide cells with increased resistance to compounds active against the gene product expressed by the modified allele of the target gene.

In yet another embodiment of the present invention, the strains constructed according to the methods disclosed are used for the screening of therapeutic agents effective for the treatment of non-infectious diseases in a plant or an animal, such as a human. As a consequence of the similarity of a target's amino acid sequence with a plant or animal counterpart, or the lack of sequence similarity, active compounds so identified may have therapeutic applications for the treatment of diseases in the plant or animal, in particular, human diseases, such as cancers and immune disorders.

The present invention, in other embodiments, further encompasses the use of transcriptional profiling and proteomics techniques to analyze the expression of essential and/or virulence genes under a variety of conditions, including in the presence of known drugs. The information yielded from such studies can be used to uncover the target and mechanism of known drugs, to discover new drugs that act in a similar fashion to known drugs, and to delineate the interactions between gene products that are essential to growth and survival of the organism and that are instrumental to virulence and pathogenicity of the organism.

In a further embodiment of the present invention, a set of genes of a pathogenic organism are identified as potential targets for drug screening. Such genes comprise, genes that have been determined, using the methods and criteria disclosed herein, to be essential for survival of a pathogenic fungus and/or for the virulence and/or pathogenicity of the pathogenic fungus. The polynucleotides of the essential genes or virulence genes of a pathogenic organism (i.e., the target genes) provided by the present invention can be used by various drug discovery purposes. Without limitation, the polynucleotides can be used to express recombinant protein for characterization, screening

or therapeutic use; as markers for host tissues in which the pathogenic organisms invade or reside (either permanently or at a particular stage of development or in a disease states); to compare with DNA sequences of other related or distant pathogenic organisms to identify potential orthologous essential or virulence genes; for selecting and making oligomers for attachment to a nucleic acid array for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; as an antigen to raise anti-DNA antibodies or elicit another immune response; and as a therapeutic agent (e.g., antisense). Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in assays to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The polypeptides or proteins encoded by the essential genes and virulence genes (i.e. the target gene products) provided by the present invention can also be used in assays to determine biological activity, including its uses as a member in a panel or an array of multiple proteins for high-throughput screening; to raise antibodies or to elicit immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as a marker for host tissues in which the pathogenic organisms invade or reside (either permanently or at a particular stage of development or in a disease states); and, of course, to isolate correlative receptors or ligands (also referred to as binding partners) especially in the case of virulence factors. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction, such as those involved in invasiveness, and pathogenicity of the pathogenic organism.

Any or all of these drug discovery utilities are capable of being developed into a kit for commercialization as research products. The kits may comprise polynucleotides and/or polypeptides corresponding to a plurality of essential genes and virulence genes of the invention, antibodies, and/or other reagents.

4. BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the URA blaster method for gene disruption in *Candida albicans*.

5 Figure 2 depicts the GRACE method for constructing a gene disruption of one allele of a gene (*CaKRE9*), and promoter replacement of the second allele of the target gene, placing the second allele under conditional, regulated control by a heterologous promoter.

10 Figure 3 presents conditional gene expression , using GRACE technology, with *KRE1*, *KRE5*, *KRE6* and *KRE9*.

Figure 4 presents conditional gene expression using GRACE technology with *CaKRE1*, *CaTUB1*, *CaALG7*, *CaAUR1*, *CaFKS1* and *CaSAT2*.

15 Figure 5 presents a Northern Blot Analysis of *CaHIS3*, *CaALR1*, *CaCDC24* and *CaKRE9* mRNA isolated from GRACE strains to illustrate elevated expression under non-repressing conditions.

20 Figure 6 presents growth of a *CaHIS3* heterozygote strain and a tetracycline promoter-regulated *CaHIS3* GRACE strain compared to growth of a wild-type diploid *CaHIS3* strain in the presence and absence of 3-aminotriazole (3-AT).

Figure 6A depicts growth of a wild-type strain and a *CaHIS3* heterozygote
25 strain as compared with a *CaHIS3* GRACE strain constitutively expressing the tetracycline promoter-regulated imidazoleglycerol phosphate dehydratase, in the presence of inhibitory levels of 3-aminotriazole.

Figure 6B depicts growth of a wild-type strain, a haploinsufficient *CaHIS3*
30 heterozygote strain, and a *CaHIS3* GRACE strain constitutively expressing the tetracycline promoter-regulated imidazoleglycerol phosphate dehydratase, in the presence of an intermediate level of 3-aminotriazole.

Figure 6C depicts growth of a wild-type strain, a haploinsufficient *CaHIS3*
35 heterozygote strain, and a *CaHIS3* GRACE strain minimally expressing the tetracycline

promoter-regulated imidazoleglycerol phosphate dehydratase, in the presence of an intermediate level of 3-aminotriazole.

Figure 6D demonstrates the hypersensitivity of the *CaHIS3* GRACE strain minimally expressing the tetracycline promoter-regulated imidazoleglycerol phosphate dehydratase, in the presence of an intermediate level of 3-aminotriazole.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Gene Disruption And Drug Target Discovery

The present invention provides a systematic and efficient method for drug target identification and validation. The approach is based on genomics information as well as the biological function of individual genes.

The methods of the invention generates a collection of genetic mutants in which the dosage of specific genes can be modulated, such that their functions in growth, survival, and/or pathogenicity can be investigated. The information accrued from such investigations allows the identification of individual gene products as potential drug targets. The present invention further provides methods of use of the genetic mutants either individually or as a collection in drug screening and for investigating the mechanisms of drug action.

Generally, in gene disruption experiments, the observation that homozygous deletions cannot be generated for both alleles of a gene in a diploid organism, cannot, *per se*, support the conclusion that the gene is an essential gene. Rather, a direct demonstration of expression of the gene in question that is coupled with viability of the cell carrying that gene, is required for the unambiguous confirmation that the gene in question is essential.

A direct demonstration that a given gene is essential for survival of a cell can be established by disrupting its expression in diploid organisms which have a haploid stage. For example, in *Saccharomyces cerevisiae*, this is achieved by complete removal of the gene product through gene disruption methods in a diploid cell type, followed by sporulation and tetrad dissection of the meiotic progeny to enable direct comparison of haploid yeast strains possessing single mutational differences. However, such an approach is not applicable to asexual yeast strains, which include most diploid pathogenic cell types, and alternative methods are required for eliminating expression of a putative essential gene.

In one embodiment, the invention provides a method for creating a diploid mutant cell of an organism in which the dosage of a specific gene can be modulated. By this method of the invention, one allele of a target gene in a diploid cell of an organism is disrupted while the second allele is modified by having its promoter replaced by a regulated promoter of heterologous origin. A strain constructed in this manner is said to comprise a modified allelic pair, i.e., a gene wherein both alleles are modified as described above. Where the genomic DNA sequence of the organism is available, this process may be repeated with each and every gene of the organism, thereby constructing a collection of mutant organisms each harboring a disrupted allele and an allele which can be conditionally expressed. This gene disruption strategy, therefore, provides a substantially complete set of potential drug target genes for that organism. This collection of mutant organisms, comprising a substantially complete set of modified allelic pairs, forms the basis for the development of high throughput drug screening assays. A collection of such mutant organisms can be made even when the genomic sequences of an organism are not completely sequenced. It is contemplated that a smaller collection of mutant organisms can be made, wherein in each mutant organism, one allele of a desired subset of gene is disrupted, and the other allele of the genes in this subset is placed under conditional expression. The method of the invention employed for the construction of such strains is referred to herein as the GRACE method, where the acronym is derived from the phrase gene replacement and conditional expression.

The GRACE method, which involves disruption of one allele coupled with conditional expression of the other allele, overcomes limitations relying upon repeated cycles of disruption with the URA blaster cassette followed by counterselection for its loss. The GRACE method permits large scale target validation in a diploid pathogenic microorganism, such as a pathogenic fungus.

The GRACE method of the invention, as applied to a diploid cell involves two steps: (i) gene replacement resulting in disruption of the coding and/or non-coding region(s) of one wild type allele by insertion, truncation, and/or deletion, and (ii) conditional expression of the remaining wild type allele via promoter replacement or conditional protein instability (Fig. 2). Detailed descriptions of the method is provided in later sections.

Isolated mutant organisms resulting from the application of the GRACE method are referred to herein as GRACE strains of the organism. Such mutant strains of an organism are encompassed by the invention. In a particular embodiment, a collection of GRACE strains which are generated by subjecting substantially all the different genes in the genome of the organism to modification by the GRACE method is provided. In this

collection, each strain comprises the modified alleles of a different gene, and substantially all the genes of the organism are represented in the collection. It is intended that a GRACE strain is generated for every gene in an organism of interest. Alternatively, a smaller collection of GRACE strains of an organism can be generated wherein a desired subset of the genes in the organism are modified by the GRACE method.

A gene is generally considered essential when viability and/or normal growth of the organism is substantially coupled to or dependent on the expression of the gene. An essential function for a cell depends in part on the genotype of the cell and in part the cell's environment. Multiple genes are required for some essential function, for example, energy metabolism, biosynthesis of cell structure, replication and repair of genetic material, etc. Thus, the expression of many genes in an organism are essential for its growth and/or survival. Accordingly, when the viability or normal growth of a GRACE strain under a defined set of conditions is coupled to or dependent on the conditional expression of the remaining functional allele of a modified allelic gene pair, the gene which has been modified in this strain by the GRACE method is referred to as an "essential gene" of the organism.

A gene is generally considered to contribute to the virulence/pathogenicity of an organism when pathogenicity of the organism is associated at least in part to the expression of the gene. Many genes in an organism are expected to contribute to the virulence and/or pathogenicity of the organism. Accordingly, when the virulence and/or pathogenicity of a GRACE strain to a defined host or to defined set of cells from a host is associated with the conditional expression of the remaining functional allele of a modified allelic gene pair, the gene which has been modified in this strain by the GRACE method is referred to as a "virulence gene" of the organism.

The present invention provides a convenient and efficient method to identify essential genes of a pathogenic organism, and to validate their usefulness in drug discovery programs. The method of the invention can similarly be used to identify virulence genes of a pathogenic organism. The identities of these essential genes and virulence genes of an organism as identified by the GRACE method are encompassed in the present invention. Substantially all of the essential genes and virulence genes of an organism can be identified and validated by the GRACE method of the invention.

Each of the essential genes and virulence genes so identified represent a potential drug target for the organism, and can be used individually or as a collection in various methods of drug screening. Depending on the objective of the drug screening program and the target disease, the essential genes and virulence genes of the invention can

be classified and divided into subsets based on the structural features, functional properties, and expression profile of the gene products. The gene products encoded by the essential genes and virulence genes within each subset may share similar biological activity, similar intracellular localization, structural homology, and/or sequence homology. Subsets may also be created based on the homology or similarity in sequence to other organisms in a similar or distant taxonomic group, *e.g.* homology to *Saccharomyces cerevisiae* genes, or to human genes, or a complete lack of sequence similarity or homology to genes of other organisms, such as *S. cerevisiae* or human. Subsets may also be created based on the display of cidal terminal phenotype or static terminal phenotype by the organism bearing the modified gene. Such subsets, referred to as essential gene sets or virulence gene sets, which can be conveniently investigated as a group in a drug screening program, are provided by the present invention. Accordingly, the present invention provides a plurality of mutant organisms, such as a collection of GRACE strains, each comprising the modified alleles of a different gene, wherein each gene is essential for the growth and/or survival of the cells.

In a specific embodiment, substantially all of the essential genes in the genome of a pathogenic fungus are identified by the GRACE method, and the GRACE strains containing the modified allelic pairs of essential genes are included in a collection of GRACE strains. In another specific embodiment, substantially all of the virulence genes in the genome of a pathogenic fungus are identified by the GRACE method, and the GRACE strains containing the modified allelic pairs of virulence genes are included in a collection of GRACE strains.

For *Candida albicans*, a GRACE strain collection for the entire genome may comprise approximately 7000 modified allelic pairs of genes based on analysis of the *C. albicans* genome sequence. The complete set of essential genes of *C. albicans* is estimated to comprise approximately 1000 genes. The present invention provides the identities of some of these genes in *C. albicans*, and the various uses of these genes and their products as drug targets. In addition, estimates as to the number of genes participating in the virulence of this pathogen range between 100 and 400 genes. Once the identity of an essential gene is known, various types of mutants containing one or more copies of the mutated essential gene created by other methods beside the GRACE method are contemplated and encompassed by the invention.

The invention also provides biological and computational methods, and reagents that allow the isolation and identification of genes that are homologous to the identified essential and virulence genes of *C. albicans*. Information obtained from the GRACE strains of diploid organisms can be used to identify homologous sequences in

haploid organisms. The identities and uses of such homologous genes are also encompassed by the present invention.

For clarity of discussion, the invention is described in the subsections below by way of example for the pathogenic fungus, *Candida albicans*. However, the principles
5 may be analogously applied to the essential and virulence genes of other pathogens and parasites, of plants and animals including humans. The GRACE method can be applied to any pathogenic organisms that has a diploid phase in their life cycles. Hence, the term diploid pathogenic organism is not limited to organism that exist exclusively in diploid form, but encompasses also organisms that have both haploid and diploid phases in their life
10 cycle.

For example, the GRACE method for drug target identification and validation can be directly applied to other pathogenic fungi. *Deuteromycetous* fungi, i.e. those lacking a sexual cycle and classical genetics, (in which *C. albicans* is included), represent the majority of human fungal pathogens. *Aspergillus fumigatus* is another
15 medically-significant member of this phylum, which, more strictly, includes members of the *Ascomycota* and the *Basidiomycota*. *A. fumigatus*, an *Ascomycete* is the predominant air borne infectious fungal agent causing respiratory infection, or invasive aspergillosis (IA), in immunocompromised patients. While relatively unknown 20 years ago, today the number of IA cases is estimated to be several thousand per year. Moreover, IA exhibits a mortality
20 rate exceeding 50% and neither amphotericin B nor fluconazole are highly efficacious. Compounding these problems is that identification of novel drug targets is limited by the current state of target validation in this organism.

The GRACE method demonstrated for *C. albicans* is readily adapted for use with *A. fumigatus*, for the following reasons. Although, *A. fumigatus* possesses a haploid
25 genome, the GRACE method could be simplified to one step-conditional promoter replacement of the wild type promoter. Since *A. fumigatus*, in contrast to *Candida albicans*, adheres to the universal genetic code, extensive site-directed mutagenesis, like that required to engineer the GRACE method for *C. albicans*, would not be required. Moreover, essential molecular biology techniques such as transformation and gene disruption *via* homologous
30 recombination have been developed for *A. fumigatus*. Selectable markers are available for these techniques in *A. fumigatus*, and include genes conferring antibiotic resistance to hygromycin B and phleomycin, and the auxotrophic marker, *ura3*. Furthermore, both public and private *A. fumigatus* genome sequencing projects exist. Therefore, sequence
35 information is available both for the identification of putative essential genes as well as for the experimental validation of these drug targets using the GRACE method. Additional

pathogenic *deuteromycetous* fungi to which the GRACE method may be applied include *Aspergillus flavus*, *Aspergillus niger*, and *Coccidioides immitis*.

In another aspect of the present invention, the GRACE method for drug target identification and validation is applied to *Basidiomycetous* pathogenic fungi. One particular, medically-significant member of this phylum is *Cryptococcus neoformans*. This air borne pathogen represents the fourth (7-8%) most commonly recognized cause of life-threatening infections in AIDS patients. Transformation and gene disruption strategies exist for *C. neoformans* and a publically funded genome sequencing project for this organism is in place. *C. neoformans* possesses a sexual cycle, thus enabling the GRACE method to be employed with both haploid and diploid strains. Other medically-significant *Basidiomycetes* include *Trichosporon beigelii* and *Schizophyllum commune*.

In the same way medically relevant fungal pathogens are suitable for a rational drug target discovery using the GRACE method, so too may plant fungal pathogens and animal pathogens be examined to identify novel drug targets for agricultural and veterinary purposes. The quality and yield of many agricultural crops including fruits, nuts, vegetables, rice, soybeans, oats, barley and wheat are significantly reduced by plant fungal pathogens. Examples include the wheat fungal pathogens causing leaf blotch (*Septoria tritici*), glume blotch (*Septoria nodorum*), various wheat rusts (*Puccinia recondita*, *Puccinia graminis*); powdery mildew (various species), and stem/stock rot (*Fusarium spp.*) Other particularly destructive examples of plant pathogens include, *Phytophthora infestans*, the causative agent of the Irish potato famine, the Dutch elm disease causing ascomycetous fungus, *Ophiostoma ulmi*, the corn smut causing pathogen, *Ustilago maydis* and the rice-blast-causing pathogen *Magnaporthe grisea*. The emerging appearance of fungicidal-resistant plant pathogens and increasing reliance on monoculture practices, clearly indicate a growing need for novel and improved fungicidal compounds. Accordingly, the present invention encompasses the application of the GRACE method to identify and validate drug targets in pathogens and parasites of plants and livestock. Table I lists exemplary groups of haploid and diploid fungi of medical, agricultural, or commercial value.

Table I: Exemplary Haploid and Diploid Fungi

Ascomycota		
<u>Animal pathogens:</u>	<u>Plant Pathogens:</u>	<u>General Commercial Significance</u>
5 <i>Aspergillus fumigatus</i> <i>Alternaria spp</i> <i>Blastomyces dermatidis</i> <i>Candida spp</i> including <i>Candida dublinensis</i> <i>Candida glabrata</i>	<i>Alternaria solanii</i> <i>Gaeumannomyces graminis</i> <i>Cercospora zeae-maydis</i> <i>Botrytis cinerea</i> <i>Claviceps purpurea</i> <i>Corticium rolfsii</i>	<i>Aspergillus niger</i> <i>Schizosaccharomyces pombe</i> <i>Pichia pastoris</i> <i>Hansenula polymorpha</i> <i>Ashbya gossipii</i> <i>Aspergillus nidulans</i>
10 <i>Candida krusei</i> <i>Candida lusitanae</i> <i>Candida parapsilopsis</i> <i>Candida tropicalis</i> <i>Coccidioides immitis</i> <i>Exophiala dermatitidis</i> <i>Fusarium oxysporum</i>	<i>Endothia parasitica</i> <i>Sclerotinia sclerotiorum</i> <i>Erysiphe graminis</i> <i>Erysiphe triticii</i> <i>Fusarium spp.</i> <i>Magnaporthe grisea</i> <i>Plasmopara viticola</i>	<i>Trichoderma reesei</i> <i>Aureobasidium pullulans</i> <i>Yarrowia lipolytica</i> <i>Candida utilis</i> <i>Kluyveromyces lactis</i>
15 <i>Histoplasma capsulatum</i> <i>Pneumocystis carinii</i>	<i>Penicillium digitatum</i> <i>Ophiostoma ulmi</i> <i>Rhizoctonia species including oryzae</i> <i>Septoria species including</i> <i>Septoria avenae</i> <i>Septoria nodorum</i> <i>Septoria passerinii</i> <i>Septoria triticii</i>	
20	<i>Venturia inaequalis</i> <i>Verticillium dahliae</i> <i>Verticillium albo-atrum</i>	
Basidiomycota		
<u>Animal pathogens:</u>	<u>Plant Pathogens:</u>	<u>General commercial significance</u>
25 <i>Cryptococcus neoformans</i> <i>Trichosporon beigelii</i>	<i>Puccinia spp</i> including <i>Puccinia coronata</i> <i>Puccinia graminis</i> <i>Puccinia recondita</i> <i>Puccinia striiformis</i>	<i>Agaricus campestris</i> <i>Phanerochaete chrysosporium</i> <i>Gloeophyllum trabeum</i> <i>Trametes versicolor</i>
30	<i>Tilletia spp</i> including <i>Tilletia caries</i> <i>Tilletia controversa</i> <i>Tilletia indica</i> <i>Tilletia tritici</i> <i>Tilletia foetida</i> <i>Ustilago maydis</i>	
35	<i>Ustilago hordei</i>	

ZygomycotaAnimal pathogens:Plant Pathogens:General commercial
significance*Absidia corymbifera**Mucor rouxii*5 *Rhizomucor pusillus**Rhizopus arrhizus*

All *Candida* species except *Candida glabrata* are obligate diploid species that lack a haploid phase in its life cycle, and are thus subject to the application of the GRACE methods.

10

5.2 Construction of GRACE Strains

According to the invention, in a GRACE strain of a diploid organism, only one allele of a gene is eliminated, while the second allele is placed under the control of the heterologous promoter, the activity of which is regulatable. Where the gene is essential, elimination of both alleles will be lethal or severely crippling for growth. Therefore, in the present invention, a heterologous promoter is used to provide a range of levels of expression of the second allele. Depending on the conditions, the second allele can be non-expressing, underexpressing, overexpressing, or expressing at a normal level relative to that when the allele is linked to its native promoter. A heterologous promoter is a promoter from a different gene from the same pathogenic organism, or it can be a promoter from a different species.

Precise replacement of a target gene is facilitated by using a gene disruption cassette comprising a selectable marker, preferably a dominant selectable marker, that is expressible in the strain of interest. The availability of two distinct dominant selectable markers allows the gene replacement process to be engineered at both alleles of the target gene, without the required counterselection step inherent in existing methods.

In particular, the present invention encompasses a method for constructing a strain of diploid pathogenic fungal cells, in which both alleles of a gene are modified, the method comprising the steps of (a) modifying a first allele of a gene in diploid pathogenic fungal cells by recombination using a gene disruption cassette comprising a nucleotide sequence encoding a selectable marker that is expressible in the cells, thereby providing heterozygous pathogenic fungal cells in which the first allele of the gene is inactivated; and (b) modifying the second allele of the gene in the heterozygous diploid pathogenic fungal cells by recombination with a promoter replacement fragment comprising a heterologous promoter, such that the expression of the second allele of the gene is regulated by the heterologous promoter.

The process can be repeated for a desired subset of the genes such that a collection of GRACE strains is generated wherein each strain comprises a modified allelic pair of a different gene. By repeating this process for every gene in a pathogenic fungus, a complete set of GRACE strains representing the entire genome of the pathogenic fungus can be obtained. Thus, the present invention provides a method of assembling a collection of diploid pathogenic fungal cells, each of which comprises the modified alleles of a different gene. The method comprises repeating the steps of modifying pairs of alleles a plurality of times, wherein a different pair of gene alleles is modified with each repetition, thereby providing the collection of diploid pathogenic fungal cells each comprising the modified alleles of a different gene.

A preferred embodiment for the construction of GRACE strains, uses the following two-step method. *C. albicans* is used as an example.

5.2.1 Heterozygote Construction By Gene Disruption

Several art-known methods are available to create a heterozygote mutant. In less preferred embodiments, auxotrophic markers, such as but not limited to *CaURA3*, *CaHIS3*, *CaLEU2*, or *CaTRP1*, could be used for gene disruption if desired. However, the preferred method of heterozygote construction in diploid fungi employs a genetically modified dominant selectable marker. *C. albicans* is sensitive to the nucleoside-like antibiotic streptothricin at a concentration of 200 micrograms per milliliter. The presence of the *Escherichia coli* SAT1 gene within *C. albicans* allows acetylation of the drug rendering it nontoxic and permitting the strain to grow in the presence of streptothricin at a concentration of 200 micrograms per milliliter. Expression of the SAT1 gene in *C. albicans* is made possible by engineering the gene so that its DNA sequence is altered to conform to the genetic code of this organism and by providing a *CaACT1* promoter (Morschhauser et al. (1998) Mol. Gen. Genet. 257:412-420) and a *CaPCK1* terminator sequence (Leuker et al. (1997) Gene 192: 235-40). This genetically modified marker is referred to as *CaSAT1* which is the subject of a copending United States nonprovisional application, filed February 16, 2001.

C. albicans is also sensitive to a second fungicidal compound, blasticidin, whose cognate resistance gene from *Bacillus cereus*, BSR, has similarly been genetically engineered for expression in *C. albicans* (*CaBSR1*), and has been shown to confer a dominant drug resistance phenotype. PCR amplification of either dominant selectable marker so as to include about 65 bp of flanking sequence identical to the sequence 5' and 3'

of the *C. albicans* gene to be disrupted, allows construction of a gene disruption cassette for any given *C. albicans* gene.

By employing the method of Baudin et al. (1993, Nucleic Acids Research 21:3329-30), a gene disruption event can be obtained following transformation of a *C. albicans* strain with the PCR-amplified gene disruption cassette and selection for drug resistant transformants that have precisely replaced the wild type gene with the dominant selectable marker. Such mutant strains can be selected for growth in the presence of a drug, such as but not limited to streptothricin. The resulting gene disruptions are generally heterozygous in the diploid *C. albicans*, with one copy of the allelic pair on one homologous chromosome disrupted, and the other allele on the other homologous chromosome remaining as a wild type allele as found in the initial parental strain. The disrupted allele is non-functional, and expression from this allele of the gene is nil. By repeating this process for all the genes in the genome of an organism, a set of gene disruptions can be obtained for every gene in the organism. The method can also be applied to a desired subset of genes.

5.2.2 Conditional Expression By a Tetracycline-Regulatable Promoter

The conditional expression system used in this embodiment of the invention comprises a regulatable promoter and a means for regulating promoter activity. Conditional expression of the remaining wild type allele in a heterozygote constructed as set forth in Section 5.1.1 is achieved by replacing its promoter with a tetracycline-regulatable promoter system that is developed initially for *S. cerevisiae* but which is modified for use in *C. albicans*. See Gari et al., 1997, Yeast 13:837-848; and Nagahashi et al., 1997, Mol. Gen. Genet. 255:372-375.

Briefly, conditional expression is achieved by first constructing a transactivation fusion protein comprising the *E. coli* TetR tetracycline repressor domain or DNA binding domain (amino acids 1-207) fused to the transcription activation domain of *S. cerevisiae* GAL4 (amino acids 785-881) or HAP4 (amino acids 424-554). Multiple CTG codon corrections were introduced to comply with the *C. albicans* genetic code. The nucleotide sequences encoding the transactivation fusion proteins of *E. coli* TetR (amino acids 1-207) plus *S. cerevisiae* GAL4 (amino acids 785-881), and of *E. coli* TetR (amino acids 1-207) plus *S. cerevisiae* HAP4 (amino acids 424-554), both of which have been modified for proper expression in *C. albicans* are encompassed by the present invention. Accordingly, the invention provides haploid or diploid cells that can comprise a nucleotide sequence encoding a transactivation fusion protein expressible in the cells, wherein the transactivation fusion protein comprises a DNA binding domain and a transcription

activation domain.

Constitutive expression of the transactivation fusion protein in *C. albicans* can be achieved by providing a *CaACT1* promoter and *CaACT1* terminator sequence. However, it will be appreciated that any regulatory regions, promoters and terminators, that are functional in *C. albicans* can be used to express the fusion protein. Thus, a nucleic acid molecule comprising a promoter functional in *C. albicans*, the coding region of a transactivation fusion protein, and a terminator functional in *C. albicans*, are encompassed by the present invention. Such a nucleic acid molecule can be a plasmid, a cosmid, a transposon, or a mobile genetic element. In a preferred embodiment, the TetR-Gal4 or TetR-Hap4 transactivators can be stably integrated into a *C. albicans* strain, by using either *ura3* and *his3* auxotrophic markers.

In this embodiment, the invention further provides that a promoter replacement fragment comprising a nucleotide sequence encoding heterologous promoter which comprises at least one copy of a nucleotide sequence which is recognized by the DNA binding domain of the transactivation fusion protein, and wherein binding of the transactivation fusion protein increases transcription of the heterologous promoter. The heterologous tetracycline promoter initially developed for *S. cerevisiae* gene expression, contains an *ADHI* 3' terminator sequence, variable number of copies of the tetracycline operator sequence (2, 4, or 7 copies), and the *CYCI* basal promoter. The tetracycline promoter has been subcloned adjacent to both *CaHIS3* and *CaSAT1* selectable markers in the orientation favoring tetracycline promoter-dependent regulation when placed immediately upstream the open reading frame of the gene of interest. PCR amplification of the *CaHIS3*-Tet promoter cassette incorporates 65bp of flanking sequence homologous to the promoter sequence around nucleotide positions -200 and -1 (relative to the start codon) of the target gene, thereby producing a conditional promoter replacement fragment for transformation. When transformed into a *C. albicans* strain made heterozygous as described in Section 5.1.1 using the *CaSAT1* disruption cassette, homologous recombination between the promoter replacement fragment and the promoter of the wild type allele generates a strain in which the remaining wild type gene is conditionally regulated gene by the tetracycline promoter. Transformants are selected as His prototrophs and verified by Southern blot and PCR analysis.

In this particular embodiment, the promoter is induced in the absence of tetracycline, and repressed by the presence of tetracycline. Analogs of tetracycline, including but not limited to chlortetracycline, demeclocycline, doxycycline, meclocycline, methocycline, minocycline hydrochloride, anhydrotetracycline, and oxytetracycline, can also

be used to repress the expression of the modified gene allele in a GRACE strain.

The present invention also encompasses alternative variants of the tetracycline promoter system, based upon a mutated tetracycline repressor (tetR) molecule, designated tetR', which is activated (*i.e.* binds to its cognate operator sequence) by binding
5 of the antibiotic effector molecule to promote expression, and is repressed (*i.e.* does not bind to the operator sequence) in the absence of the antibiotic effectors, when the tetR' is used instead of, or in addition to, the wild-type tetR. For example, the GRACE method could be performed using tetR' instead of tetR in cases where repression is desired under conditions which lack the presence of tetracycline, such as shut off of a gene participating in
10 drug transport (*e.g.* CaCDR1, CaPDR5, or CaMDR1). Also, the GRACE method could be adapted to incorporate both the tetR and tetR' molecules in a dual activator/repressor system where tetR is fused to an activator domain and tetR' is fused to a general repressor (*e.g.* CaSsr6 or CaTup1) to enhance or further repress expression in the presence of the antibiotic effector molecules (Belli et al., 1998, Nucl Acid Res 26:942-947 which is incorporated
15 herein by reference). These methods of providing conditional expression are also contemplated.

In another embodiment of the invention, the method may also be applied to haploid pathogenic fungi by modifying the single allele of the gene via recombination of the allele with a promoter replacement fragment comprising a nucleotide sequence encoding a
20 heterologous promoter, such that the expression of the gene is conditionally regulated by the heterologous promoter. By repeating this process for a preferred subset of genes in a haploid pathogenic organism, or its entire genome, a collection or a complete set of conditional mutant strains can be obtained. A preferred subset of genes comprises genes that share substantial nucleotide sequence homology with target genes of other organisms,
25 *e.g.*, *C. albicans* and *S. cerevisiae*. For example, this variation to the method of the invention may be applied to haploid fungal pathogens including, but not limited to, animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida glabrata*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*, *Trichosporon*
30 *beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recondita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species.

The means to achieve conditional expression are not restricted to the
35 tetracycline promoter system and can be performed using other conditional promoters. Such

conditional promoter may, for example, be regulated by a repressor which repress transcription from the promoter under particular condition or by a transactivator which increases transcription from the promoter, such as, when in the presence of an inducer. For example, the *C. albicans* *CaPCK1* promoter is not transcribed in the presence of glucose but
5 has a high level of expression in cells grown on other carbon sources, such as succinate, and therefore could also be adopted for conditional expression of the modified allele in a GRACE strain. To this end, it has been shown that both *CaHIS1* and *CaSAT1* are essential for growth on glucose-containing medium using the *CaPCK1* promoter as an alternative to the tetracycline promoter in the above description. In this instance, the *CaPCK1* promoter
10 is heterologous to the gene expressed and not to the organism, and such heterologous promoters are also encompassed in the invention. Alternative promoters that could functionally replace the tetracycline promoter include but are not limited to other antibiotic-based regulatable promoter systems (e.g., pristinamycin-induced promoter or PIP) as well as *Candida albicans* conditionally-regulated promoters such as *MET25*, *MAL2*, *PHO5*,
15 *GAL1,10*, *STE2*, or *STE3*.

In a preferred embodiment of the GRACE method, performing the gene disruption first enables heterozygous strains to be constructed and separately collected as a heterozygote strain collection during the process of drug target validation. Such a
C. albicans heterozygote strain collection enables drug screening approaches based on
20 haploinsufficiency for validated targets within the collection. As used herein, the term “haploinsufficiency” refers to the phenomenon whereby heterozygous strains for a given gene express approximately half the normal diploid level of a particular gene product. Consequently, these strains provide constructions having a diminished level of the encoded gene product, and they may be used directly in screens for antifungal compounds. Here
25 differential sensitivity of a diploid parent, as compared with its heterozygous derivative, will indicate that a drug is active against the encoded gene product.

It is clear to those skilled in the art that the order of allele modification followed in this embodiment of the invention is not critical, and that it is feasible to perform these steps in a different order such that the conditional-expressing allele is constructed first
30 and the disruption of the remaining wild type gene allele be performed subsequently. However, where the promoter replacement step is carried out first, care should be taken to delete sequences homologous to those employed in the gene disruption step.

A specific application of the GRACE method, as used to construct modified alleles of the target gene *CaKRE9* is provided in Section 6.

35

5.2.3 Alternative Methods of Conditional Expression

In other embodiments of the invention, conditional expression could be achieved by means other than the reliance of conditional promoters. For example, conditional expression could be achieved by the replacement of the wild type allele in
5 heterozygous strains with temperature sensitive alleles derived *in vitro*, and their phenotype would then be analyzed at the nonpermissive temperature. In a related approach, insertion of a ubiquitination signal into the remaining wild type allele to destabilize the gene product during activation conditions can be adopted to examine phenotypic effects resulting from gene inactivation. Collectively, these examples demonstrate the manner in which *C.*
10 *albicans* genes can be disrupted and conditionally regulated using the GRACE method.

In an alternative embodiment of the present invention, a constitutive promoter regulated by an excisable transactivator can be used. The promoter is placed upstream to a target gene to repress expression to the basal level characteristic of the promoter. For example, in a fungal cell, a heterologous promoter containing *lexA* operator
15 elements may be used in combination with a fusion protein composed of the *lexA* DNA binding domain and any transcriptional activator domain (e.g. GAL4, HAP4, VP16) to provide constitutive expression of a target gene. Counterselection mediated by 5-FOA can be used to select those cells which have excised the gene encoding the fusion protein. This procedure enables an examination of the phenotype associated with repression of the target
20 gene to the basal level of expression provided by the *lexA* heterologous promoter in the absence of a functional transcription activator. The GRACE strains generated by this approach can be used for drug target validation as described in detail in the sections below. In this system, the low basal level expression associated with the heterologous promoter is critical. Thus, it is preferable that the basal level of expression of the promoter is low to
25 make this alternative shut-off system more useful for target validation.

Alternatively, conditional expression of a target gene can be achieved without the use of a transactivator containing a DNA binding, transcriptional activator domain. A cassette could be assembled to contain a heterologous constitutive promoter downstream of, for example, the *URA3* selectable marker, which is flanked with a direct
30 repeat containing homologous sequences to the 5' portion of the target gene. Additional homologous sequences upstream of the target, when added to this cassette would facilitate homologous recombination and replacement of the native promoter with the above-described heterologous promoter cassette immediately upstream of the start codon of the target gene or open reading frame. Conditional expression is achieved by selecting strains, by using
35 5-FOA containing media, which have excised the heterologous constitutive promoter and

URA3 marker (and consequently lack those regulatory sequences upstream of the target gene required for expression of the gene) and examining the growth of the resulting strain *versus* a wild type strain grown under identical conditions.

5 5.3 Identification of Essential Genes and Virulence Genes

5.3.1 Essential Genes

The present invention provides methods for determining whether the gene that has been modified in a GRACE strain is an essential gene or a virulence gene in a
10 pathogenic organism of interest. To determine whether a gene is an essential gene in an organism, a GRACE strain containing the modified alleles of the gene is cultured under conditions wherein the second modified allele of the gene which is under conditional expression, is substantially underexpressed or not expressed. The viability and/or growth of the GRACE strain is compared with that of a wild type strain cultured under the same
15 conditions. A loss or reduction of viability or growth indicates that the gene is essential to the survival of a pathogenic fungus. Accordingly, the present invention provides a method for identifying essential genes in a diploid pathogenic organism comprising the steps of culturing a plurality of GRACE strains under culture conditions wherein the second allele of each of the gene modified in the respective GRACE strain is substantially underexpressed or
20 not expressed; determining viability and/or growth indicator(s) of the cells; and comparing that with the viability and/or growth indicator(s) of wild type cells. The level of expression of the second allele can be less than 50% of the non-modified allele, less than 30%, less than 20%, and preferably less than 10%. Depending on the heterologous promoter used, the level of expression can be controlled by, for example, antibiotics, metal ions, specific
25 chemicals, nutrients, pH, temperature, etc.

Candida albicans is used herein as an example which has been analyzed by the GRACE methodology.

For example, *C. albicans* conditional gene expression using the GRACE method was performed using *CaKRE1*, *CaKRE5*, *CaKRE6*, and *CaKRE9* (Fig. 3).
30 *CaKRE5*, *CaKRE6*, and *CaKRE9* are predicted to be essential or conditionally essential (*CaKRE9* null strains are nonviable on glucose but viable on galactose), in *C. albicans* as demonstrated by gene disruption using the Ura blaster method. *CaKRE1* has been demonstrated as a nonessential gene using the Ura blaster method in *C. albicans*. Strains
35 heterozygous for the above genes were constructed by PCR-based gene disruption method using the *CaSAT1* disruption cassette followed by tetracycline regulated promoter

replacement of the native promoter of the wild type allele. Robust growth of each of these strains suggests expression proceeds normally in the absence of tetracycline. When tetracycline is added to the growth medium, expression of these tetracycline promoter-regulated genes is greatly reduced or abolished. In the presence of tetracycline, the GRACE strain cells containing each one of the three essential *C. albicans* genes cited above stop growing. As expected, only the *CaKRE1* GRACE strain demonstrates robust growth despite repression of *CaKRE1* expression.

To further examine the utility of the GRACE method in target validation, growth of four additional GRACE strains controlling expression of the known essential genes *CaTUB1*, *CaALG7*, *CaAUR1*, and *CaFKS1*, as well as the predicted essential gene *CaSAT2*, and *CaKRE1* were compared under inducing versus repressing conditions (Fig. 4). As expected, GRACE strains of *CaTUB1*, *CaALG7*, *CaAUR1* and *CaFKS1* failed to grow under repressing conditions, unlike the non-essential *CaKRE1* GRACE strain. Furthermore, as predicted, the *CaSAT2* GRACE strain demonstrates essentiality of this gene in *C. albicans*. The *CaSAT2* gene, which has been engineered as a dominant selectable marker for use in *C. albicans*, is a *C. albicans* gene that is homologous to a *S. cerevisiae* gene but is unrelated to the *Sat1* gene of *E. coli*.

In all cases based on other disruption data that have been generated, this is the expected response if the tetracycline regulated gene is repressed to a level where it is nonfunctional in the presence of tetracycline. Furthermore, in applying the GRACE methodology of conditional gene disruption to two additional *C. albicans* genes (*CaYPD1*, and *CaYNL194c*) whose *S. cerevisiae* counterpart is known not to be essential, no inhibition of growth was observed when these strains were incubated in the presence of tetracycline. These results establish that the method of conditional gene expression using a GRACE strain is a reliable indicator of gene essentiality.

Furthermore, the utility of the present method, as a rapid and accurate means to identifying the complete set of essential genes in *C. albicans*, has been demonstrated by an analysis of the null phenotype of a large number of genes using the GRACE two-step method of gene disruption and conditional expression. Target genes were selected as being fungal specific and essential. Such genes are referred to as target essential genes in the screening assays described below.

A literature search identified reports of URA blaster-based gene disruption experiments on a total of 89 genes, of which 13 genes were presumed to be essential, based on the inability to construct homozygous deletion strains. The 13 genes are *CaCCT8* (Rademacher et al., Microbiology, UK 144, 2951-2960 (1998)); *CaFKS1* (Mio et al., J.

Bacteriol, 179, 4096-105 (1997); and Douglas, et al., Antimicrob Agents Chemother 41, 2471-9 (1997)); *CaHSP90* (Swoboda et al., Infect Immun 63, 4506-14 (1995)); *CaKRE6* (Mio et al., J. Bacteriol 179, 2363-72 (1997)); *CaNMT1* (Weinberg et al., Mol Microbiol 16, 241-50 (1995)); *CaPRSI* (Payne et al., J. Med. Vet. Mycol. 35, 305-12 (1997)); *CaPSA1* (Care et al., Mol Microbiol 34, 792-798 (1999)); *CaRAD6* (Care et al., Mol Microbiol 34, 792-798 (1999)); *CaSEC4* (Mao et al., J. Bacteriol 181, 7235-7242 (1999)); *CaSEC14* (Monteoliva et al., Yeast 12, 1097-105 (1996)); *CaSNF1* (Petter et al., Infect Immun. 65, 4909-17 (1997)); *CaTOP2* (Keller, et al., Biochem J., 329-39 (1997)); and *CaEFT2* (Mendoza et al., Gene 229, 183-1991 (1999)). These 13 putatively essential genes and

10 *CaTUB1*, *CaALG1*, and *CaAUR1* of *C. albicans* are not initially identified by the GRACE method. However, GRACE strains containing modified alleles of any one of these 17 genes and their uses are encompassed by the invention, for example, the *CaTUB1*, *CaALG1*, and *CaAUR1* GRACE strains in Fig. 4 and the *CaKRE6* GRACE strain in Fig. 3. Any of these 17 genes may be included as a control for comparisons in the methods of the invention, or

15 as a positive control for essentiality in the collections of essential genes of the invention. The nucleic acid molecules comprising a nucleotide sequence corresponding to any of these 17 genes may be used in the methods of drug discovery of the invention as drug targets, or they may be included individually or in subgroups as controls in a kit or in a nucleic acid microarray of the invention.

20 In contrast to the use of conventional method, application of the GRACE method has already identified significantly more *C. albicans* essential genes than previously determined by the collective efforts of the entire *C. albicans* research community. The data presented herewith establishes the speed inherent to the approach of the invention and, therefore, the feasibility of extending the GRACE method to the examination of all the

25 genes of the *C. albicans* genome, the identification of the complete set of essential genes of this diploid fungal pathogen, and its application to other species.

An alternative method is available for assessing the essentiality of the modified gene in a GRACE strain. According to the invention, repression of expression of the modified gene allele within a GRACE strain may be achieved by homologous

30 recombination-mediated excision of the gene encoding the transactivator protein. In a preferred embodiment, where conditional expression of a target gene is achieved using the tetracycline-regulated promoter, constitutive expression (under nonrepressing conditions) may be repressed by homologous recombination-mediated excision of the transactivator gene (*TetR-GAL4AD*). In this way, an absolute achievable repression level is produced

35 independently of that produced by tetracycline-mediated inactivation of the transactivator

protein. Excision of the transactivator gene is made possible by virtue of the selectable marker and integration strategy used in GRACE strain construction. Stable integration of the *CaURA3*-marked plasmid containing the TetR-GAL4AD transactivator gene into the *CaLEU2* locus results in a tandem duplication of *CaLEU2* flanking the integrated plasmid.

- 5 Counterselection on 5-FOA-containing medium can then be performed to select for excision of the *CaURA3*-marked transactivator gene and to directly examine whether this alternative repression strategy reveals the target gene to be essential.

Three examples of genes defined as essential on 5-FOA containing medium but lacking any detectable growth impairment on tetracycline supplemented medium are the
10 genes, *CaYCL052c*, *CaYNL194c* and *CaYJR046c*. Presumably, this is due to the target gene exhibiting a lower basal level of expression under conditions where the transactivator gene has been completely eliminated than its gene product incompletely inactivated by addition of tetracycline. Thus, the GRACE method offers two independent approaches for the determination of whether or not a given gene is essential for viability of the host strain.

15

5.3.2 Virulence/Pathogenicity Genes

The present invention also provides methods of using the GRACE strains of a diploid pathogenic organism to identify virulence/pathogenicity genes. In addition to uncovering essential genes of a pathogenic organism, the GRACE methodology enables the
20 identification of other genes and gene products potentially relevant to the screening of drugs useful for the treatment of diseases caused by the pathogenic organism. Nonessential genes and their gene products of a pathogen which nevertheless display indispensable roles in the pathogenesis process, may therefore serve as potential drug targets for prophylactic drug development and could be used in combination with existing cidal therapeutics to improve
25 treatment strategies. Thus, genes and their products implicated in virulence and/or pathogenicity represent another important class of potential drug targets. Moreover, some of the genes implicated in virulence and pathogenicity may be species-specific, and unique to a particular strain of pathogen. It has been estimated that approximately 6-7% of the genes identified through the *C. albicans* sequencing project are absent in *S. cerevisiae*. This
30 represents as many as 420 *Candida albicans*-specific genes which potentially participate in the process of pathogenesis or virulence. Such a large scale functional evaluation of this gene set can only be achieved using the GRACE methodology of the invention.

Although essential genes provide preferred targets, value would also be placed on those nonessential *C. albicans* specific genes identified. The potential role of
35 nonessential *C. albicans*-specific genes in pathogenesis may be evaluated and prioritized

according to virulence assays (e.g. buccal epithelial cell adhesion assays and macrophage assays) and various *C. albicans* infection studies (e.g. oral, vaginal, systemic) using mouse or other animal models. In the same manner described above for essential genes, it is equally feasible to demonstrate whether nonessential genes comprising the GRACE strain collection are required for pathogenicity in a cellular assay or in a mouse model system. Accordingly, GRACE strains that fail to cause fungal infection in mice under conditions of gene inactivation by tetracycline (or alternative gene inactivation means) define the GRACE virulence/pathogenicity subset of genes. More defined subsets of pathogenicity genes, for example those genes required for particular steps in pathogenesis (e. g. adherence or invasion) can be determined by applying the GRACE pathogenicity subset of strains to *in vitro* assays which measure the corresponding process. For example, examining GRACE pathogenicity strains in a buccal adhesion or macrophage assay by conditional expression of individual genes would identify those pathogenicity factors required for adherence or cell invasion respectively. Moreover, essential genes that display substantially reduced virulence and growth rate when only partially inactivated represent "multifactorial" drug targets for which even minimally inhibitory high specificity compounds would display therapeutic value.

Accordingly, to determine whether a gene contributes toward the virulence/pathogenicity of a pathogenic organism in a host, a GRACE strain of the pathogen containing the modified alleles of the gene is allowed to infect host cells or animals under conditions wherein the second modified allele of the gene which is under conditional expression, is substantially underexpressed or not expressed. After the host cells and/or animals have been contacted with the GRACE strain for an appropriate period of time, the condition of the cells and/or animals is compared with cells and/or animals infected by a wild type strain under the same conditions. Various aspects of the infected cell's morphology, physiology, and/or biochemistry can be measured by methods known in the art. When an animal model is used, the progression of the disease, severity of the symptoms, and/or survival of the host can be determined. Any loss or reduction of virulence or pathogenicity displayed by the GRACE strain indicates that the gene modified in the strain contributes to or is critical to the virulence and/or pathogenicity of the virus. Such genes are referred to as target virulence genes in the screening assays described below.

In another aspect of the present invention, GRACE methodology can be used for the identification and delineation of genetic pathways known to be essential to the development of pathogenicity. For example, extensive work in *S. cerevisiae* has uncovered a number of processes including cell adhesion, signal transduction, cytoskeletal assembly,

that play roles in the dimorphic transition between yeast and hyphal morphologies. Deletion of orthologous genes participating in functionally homologous cellular pathways in pathogenic fungi such as *C. albicans*, *A. fumigatus*, and *C. neoformans*, has clearly demonstrated a concomitant loss of virulence. Therefore, the use of GRACE strains of orthologous genes found in *C. albicans* and other pathogenic fungi could rapidly validate potential antifungal drug target genes whose inactivation impairs hyphal development and pathogenicity.

5.3.3 Validation of Genes Encoding Drug Targets

Target gene validation refers to the process by which a gene product is identified as suitable for use in screening methods or assays in order to find modulators of the function or structure of that gene product. Criteria used for validation of a gene product as a target for drug screening, however, may be varied depending on the desired mode of action that the compounds sought will have, as well as the host to be protected.

In one aspect of the present invention, a set of GRACE strains identified and grouped as having only modified alleles of essential genes can be used directly for drug screening.

In another aspect, the initial set of essential genes is further characterized using, for example, nucleotide sequence comparisons, to identify a subset of essential genes which include only those genes specific to fungi - that is, a subset of genes encoding essential genes products which do not have homologs in a host of the pathogen, such as humans. Modulators, and preferably inhibitors, of such a subset of genes in a fungal pathogen of humans would be predicted to be much less likely to have toxic side effects when used to treat humans.

Similarly, other subsets of the larger essential gene set could be defined to include only those GRACE strains carrying modified allele pairs that do not have a homologous sequence in one or more host (e.g., mammalian) species to allow the detection of compounds expected to be used in veterinary applications. In addition, using other homology criteria, a subset of GRACE strains could be identified that would be used for the detection of anti-fungal compounds active against agricultural pathogens, inhibiting targets that do not have homologs in the crop to be protected.

Current *C. albicans* gene disruption strategies identify nonessential genes and permit the inference that other genes are essential, based on a failure to generate a homozygous null mutant. The null phenotype of a drug target predicts the absolute efficaciousness of the "perfect" drug acting on this target. For example, the difference

between a cidal (cell death) versus static (inhibitory growth) null terminal phenotype for a particular drug target. Gene disruption of *CaERG11*, the drug target of fluconazole, is presumed to be essential based on the failure to construct a homozygous *CaERG11* deletion strain using the URA blaster method. However, direct evaluation of its null phenotype
5 being cidal or static could not be performed in the pathogen, and only after the discovery of fluconazole was it possible to biochemically determine both the drug, and presumably the drug target to be static rather than as cidal. Despite the success fluconazole enjoys in the marketplace, its fungistatic mode of action contributes to its primary limitation, i.e., drug resistance after prolonged treatment. Therefore, for the first time, the ability to identify and
10 evaluate cidal null phenotypes for validated drug targets within the pathogen as provided by the invention, now enables directed strategies to identifying antifungal drugs that specifically display a fungicidal mode of action.

Using a single GRACE strain or a desired collection of GRACE strains comprising essential genes, one or more target genes can be directly evaluated as displaying
15 either a cidal or static null phenotype. This is determined by first incubating GRACE strains under repressing conditions for the conditional expression of the second allele for varying lengths of time in liquid culture, and measuring the percentage of viable cells following plating a defined number of cells onto growth conditions which relieve repression. The percentage of viable cells that remain after return to non-repressing
20 conditions reflects either a cidal (low percent survival) or static (high percent survival) phenotype. Alternatively, vital dyes such as methylene blue or propidium iodide could be used to quantify percent viability of cells for a particular strain under repressing versus inducing conditions. As known fungicidal drug targets are included in the GRACE strain collection (e.g. *CaAURI*), direct comparisons can be made between this standard fungicidal
25 drug target and novel targets comprising the drug target set. In this way each member of the target set can be immediately ranked and prioritized against an industry standard cidal drug target to select appropriate drug targets and screening assays for the identification of the most rapid-acting cidal compounds.

30

5.4 Essential Genes and Virulence Genes

5.4.1 Nucleic Acids Encoding Targets, Vectors, and Host Cells

By practice of the methods of the invention, the essentiality and the contribution to virulence of substantially all the genes in the genome of an organism can be
35 determined. The identities of essential genes and virulence genes of a diploid pathogenic

organism, such as *Candida albicans*, once revealed by the methods of the invention, allow the inventors to study their functions and evaluate their usefulness as drug targets.

Information regarding the structure and function of the gene product of the individual essential gene or virulence gene allows one to design reagents and assays to find compounds

5 that interfere with its expression or function in the pathogenic organism. Accordingly, the present invention provides information on whether a gene or its product(s) is essential to growth, survival, or proliferation of the pathogenic organism, or that a gene or its product(s) contributes to virulence or pathogenicity of the organism with respect to a host. Based on this information, the invention further provides, in various embodiments, novel uses of the
10 nucleotide and/or amino acid sequences of genes that are essential and/or that contributes to virulence or pathogenicity of a pathogenic organism, for purpose of discovering drugs that act against the pathogenic organism. Moreover, the present invention provides specifically the use of this information to identify orthologs of these essential genes in a non-pathogenic yeast, such as *Saccharomyces cerevisiae*, and the use of these orthologs in drug screening
15 methods. Although the nucleotide sequence of the orthologs of these essential genes in *S. cerevisiae* may be known, it was not appreciated that these *S. cerevisiae* genes can be useful for discovering drugs against pathogenic fungi.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising a nucleotide sequence encoding a polypeptide or a biologically
20 active ribonucleic acid (RNA). The term can further include nucleic acid molecules comprising upstream, downstream, and/or intron nucleotide sequences. The term "open reading frame (ORF)," means a series of nucleotide triplets coding for amino acids without any termination codons and the triplet sequence is translatable into protein using the codon usage information appropriate for a particular organism.

25 As used herein, the term "target gene" refers to either an essential gene or a virulence gene useful in the invention, especially in the context of drug screening. The terms "target essential gene" and "target virulence gene" will be used where it is appropriate to refer to the two groups of genes separately. However, it is expected that some genes will contribute to virulence and be essential to the survival of the organism. The target genes of
30 the invention may be partially characterized, fully characterized, or validated as a drug target, by methods known in the art and/or methods taught hereinbelow. As used herein, the term "target organism" refers to a pathogenic organism, the essential and/or virulence genes of which are useful in the invention.

The term "nucleotide sequence" refers to a heteropolymer of nucleotides,
35 including but not limited to ribonucleotides and deoxyribonucleotides, or the sequence of

these nucleotides. The terms "nucleic acid" and "polynucleotide" are also used interchangeably herein to refer to a heteropolymer of nucleotides, which may be unmodified or modified DNA or RNA. For example, polynucleotides can be single-stranded or double-stranded DNA, DNA that is a mixture of single-stranded and double-stranded regions, 5 hybrid molecules comprising DNA and RNA with a mixture of single-stranded and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising DNA, RNA, or both. A polynucleotide can also contain one or modified bases, or DNA or RNA backbones modified for nuclease resistance or other reasons. Generally, nucleic acid segments provided by this invention can be assembled from fragments of the 10 genome and short oligonucleotides, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid.

The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (*e. g.*, microbial or mammalian) expression systems. "Microbial" refers to recombinant polypeptides or 15 proteins made in bacterial or fungal (*e. g.*, yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, *e. g.*, *E. coli*, will be free of glycosylation modifications; polypeptides or proteins expressed in yeast will be glycosylated.

20 The term "expression vehicle or vector" refers to a plasmid or phage or virus, for expressing a polypeptide from a nucleotide sequence. An expression vehicle can comprise a transcriptional unit, also referred to as an expression construct, comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is 25 transcribed into mRNA and translated into protein, and which is operably linked to the elements of (1); and (3) appropriate transcription initiation and termination sequences. "Operably linked" refers to a link in which the regulatory regions and the DNA sequence to be expressed are joined and positioned in such a way as to permit transcription, and ultimately, translation. In the case of *C. albicans*, due to its unusual codon usage, 30 modification of a coding sequence derived from other organisms may be necessary to ensure a polypeptide having the expected amino acid sequence is produced in this organism. Structural units intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where a recombinant protein is expressed without a leader or transport 35 sequence, it may include an N-terminal methionine residue. This residue may or may not be

subsequently cleaved from the expressed recombinant protein to provide a final product.

The term "recombinant host cells" means cultured cells which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry stably the recombinant transcriptional unit extrachromosomally. Recombinant host cells as defined
5 herein will express heterologous polypeptides or proteins, and RNA encoded by the DNA segment or synthetic gene in the recombinant transcriptional unit. This term also means host cells which have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express RNA, polypeptides or proteins
10 endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "polypeptide" refers to the molecule form by joining amino acids to each other by peptide bonds, and may contain amino acids other than the twenty commonly used gene-encoded amino acids. The term "active polypeptide" refers to those forms of the
15 polypeptide which retain the biologic and/or immunologic activities of any naturally occurring polypeptide. The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, proteolytic processing, acetylation, carboxylation,
20 glycosylation, phosphorylation, lipidation and acylation.

The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one macromolecular component (e.g., nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight,
25 more preferably at least 99.8% by weight, of the indicated biological macromolecules present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 daltons, can be present).

Table II lists a set of fungal specific genes that are demonstrated to be essential in *C. albicans* when conditionally expressed under the tetracycline repression
30 system in the respective GRACE strains or when the gene encoding the transactivator protein is excised in the respective GRACE strain in a 5-FOA assay.

Table II

	Gene designation	DNA SeqID	Protein SeqID	Primer KOutp	Primer KODn	Primer tet up	Primer tet dn	Primer A	Primer B
	CaYBR070C (SAT2)	1	63	124	185	246	307	368	429
	CaYBR167C (POP7)	2	64	125	186	247	308	369	430
5	CaYBR243C (ALG7)	3	65	126	187	248	309	370	431
	CaYCL031C (RRP7)	4	66	127	188	249	310	371	432
	CaYDL105W	5	67	128	189	250	311	372	433
	CaYDL153C (SAS10)	6	68	129	190	251	312	373	434
	CaYDR052C (DBF4)	7	69	130	191	252	313	374	435
	CaYDR118W (APC4)	8	70	131	192	253	314	375	436
	CaYDR361C	9	71	132	193	254	315	376	437
10	CaYDR412W	10	72	133	194	255	316	377	438
	CaYDR498C (SEC20)	11	73	134	195	256	317	378	439
	CaYER026C (CHO1)	12	74	135	196	257	318	379	440
	CaYGR090W	13	75	136	197	258	319	380	441
	CaYGR245C	14	76	137	198	259	320	381	442
	CaYHR007C (ERG11)	15	77	138	199	260	321	382	443
	CaYHR036W	16	78	139	200	261	322	383	444
15	CaYHR058C (MED6)	17	79	140	201	262	323	384	445
	CaYHR118C (ORC6)	18	80	141	202	263	324	385	446
	CaYHR172W (SPC97)	19	81	142	203	264	325	386	447
	CaYHR196W	20	82	143	204	265	326	387	448
	CaYIR011C (STS1)	21	83	144	205	266	327	388	449
	CaYJL069C	22	84	145	206	267	328	389	450
	CaYJL090C (DPB11)	23	85	146	207	268	329	390	451
20	CaYJR041C	24	86	147	208	269	330	391	452
	CaYJR112W (NNF1)	25	87	148	209	270	331	392	453
	CaYKL004W (AUR1)	26	88	149	210	271	332	393	454
	CaYKL033W	27	89	150	211	272	333	394	455
	CaYKR025W (RPC37)	28	90	151	212	273	334	395	456
	CaYKR063C (LAS1)	29	91	152	213	274	335	396	457
	CaYKR071C	30	92	153	214	275	336	397	458
25	CaYKR081C	31	93	154	215	276	337	398	459
	CaYKR083C	32	94	155	216	277	338	399	460
	CaYLL003W (SF11)	33	95	156	217	278	339	400	461
	CaYLR002C	34	96	157	218	279	340	401	462
	CaYLR103C (CDC45)	35	97	158	219	280	341	402	463
	CaYLR342W (FKS1)	36	98	159	220	281	342	403	464
	CaYLR355C (ILV5)	37	99	160	221	282	343	404	465
30	CaYML025C (YML6)	38	100	161	222	283	344	405	466
	CaYML085C (TUB1)	39	101	162	223	284	345	406	467
	CaYMR149W (SWP1)	40	102	163	224	285	346	407	468
	CaYMR200W (ROT1)	41	103	164	225	286	347	408	469
	CaYMR220W (ERG8)	42	104	165	226	287	348	409	470
	CaYMR277W (FCP1)	43	105	166	227	288	349	410	471
	CaYNL132W	44	106	167	228	289	350	411	472
	CaYNL149C	45	107	168	229	290	351	412	473
35	CaYNL151C (RPC31)	46	108	169	230	291	352	413	474
	CaYNL181W	47	109	170	231	292	353	414	475

	CaYNL232W (CSL4)	48	110	171	232	293	354	415	476
	CaYNL245C	49	111	172	233	294	355	416	477
	CaYNL256W	50	112	173	234	295	356	417	478
	CaYNL260C	51	113	174	235	296	357	418	479
	CaYOR004W	52	114	175	236	297	358	419	480
5	CaYOR075W (UFE1)	53	115	176	237	298	359	420	481
	CaYOR148C (SPP2)	54	116	177	238	299	360	421	482
	CaYOR206W	55	117	178	239	300	361	422	483
	CaYOR287C	56	118	179	240	301	362	423	484
	CaYPL128C (TBF1)	57	119	180	241	302	363	424	485
	CaYPL160W (CDC60)	58	120	181	242	303	364	425	486
	CaYPL228W (CET1)	59	121	182	243	304	365	426	487
10	CaYPR165W (RHO1)	60	122	183	244	305	366	427	488
	CaYPR175W (DPB2)	61	123	184	245	306	367	428	489
	CaYPL160W (CDC60)	62	N/A	181	242	303	364	425	486

In one embodiment, the present invention provides the identities of 61 essential genes. Although the nucleotide sequence and the reading frame of a number of these genes are known, the fact that these genes are essential to the growth and/or survival of *Candida albicans* was not known until the inventors' discovery. Thus, the uses of these genes and their gene products are encompassed by the present invention. Also provided in Table II are SEQ ID NOs: that are used herein to identify the open reading frame, the deduced amino acid sequence and related oligonucleotide sequences for each identified essential gene.

Accordingly, SEQ ID NO:1 through to SEQ ID NO:62 each identifies a nucleotide sequence of the opening reading frame (ORF) of an identified essential gene. The nucleotide sequences labeled as SEQ ID NO:1-62 were obtained from a *Candida albicans* genomic sequence database version 6 assembled by the *Candida albicans* Sequencing Project and is accessible by internet at the web sites of Stanford University and University of Minnesota (See <http://www-sequence.stanford.edu:8080/> and <http://alces.med.umn.edu/Candida.html>).

The predicted amino acid sequence of the identified essential genes are set forth in SEQ ID NO:63 through to SEQ ID NO:123 which are obtained by conceptual translation of the nucleotide sequences of SEQ ID NO: 1 through to 61 once the reading frame is determined. As it is well known in the art, the codon CTG is translated to a serine residue in *C. albicans*, instead of the usual leucine in other organisms. Accordingly, the conceptual translation of the ORF is performed using the codon usage of *C. albicans*.

The DNA sequences were generated by sequencing reactions and may contain minor errors which may exist as misidentified nucleotides, insertions, and/or deletions. However, such minor errors, if present, in the sequence database should not

disturb the identification of the ORF as an essential gene of the invention. Since clones containing the ORF are available, one can readily repeat the sequencing and correct the minor error(s). Moreover, minor sequence errors do not affect the construction of GRACE strains and the uses of the GRACE strains, since these methods do not require absolute
5 sequence identity between the chromosomal DNA sequences and the sequences of the gene in the primers or recombinant DNA. In some instances, the correct reading frame of the *C. albicans* gene can be identified by comparing its overall amino acid sequence with known *S. cerevisiae* sequences.

Thus, in one embodiment of the invention, conceptual translation of the
10 nucleotide sequence of SEQ ID NO: 62 leads to an apparently premature termination of the opening reading frame when compared to its ortholog in *S. cerevisiae*. To maintain the reading frame, four nucleotides were added to create SEQ ID NO: 58 which results in the amino acid sequence of SEQ ID NO: 120. In another embodiment, the invention provides the genomic sequence of an identified essential gene, wherein the genomic sequence as set
15 forth in SEQ ID NO: 490 contains an intron. The unpublished nucleotide sequence which does not contain intron sequence and encodes a protein is set forth in SEQ ID NO: 39.

SEQ ID NO:124-486 refers to oligonucleotide primers and probes that were designed for and used in the construction of the GRACE strain for the corresponding identified essential gene. (i.e., SEQ ID NO:124-184 knockout upstream primer (KO-UP);
20 SEQ ID NO:185-245 knockout downstream primer (KO-Down); SEQ ID NO:246-306 tetracycline promoter upstream primer (Tet-Up); SEQ ID NO:307-367 Tetracycline promoter downstream primer (Tet-Down); and SEQ ID NO:368-489 primers for identification of the respective GRACE strains (primers A and B). Therefore, each set of oligonucleotides can be used to identify a unique essential gene and a unique GRACE
25 strain, e.g. by hybridization, or PCR.

The essential genes listed in Table II can be obtained using cloning methods well known to those of skill in the art, and include but are not limited to the use of appropriate probes to detect the genes within an appropriate cDNA or gDNA (genomic DNA) library. (See, for example, Sambrook et al., 1989, Molecular Cloning: A Laboratory
30 Manual, Cold Spring Harbor Laboratories, which is incorporated herein by reference in its entirety.) Probes for the sequences identified herein can be synthesized based on the DNA sequences disclosed herein in SEQ ID NO:1-62.

As used herein, "target gene" (i.e. essential and/or virulence gene) refers to
(a) a gene containing at least one of the DNA sequences and/or fragments thereof that are
35 set forth in SEQ ID NO:1 through to SEQ ID NO:62; (b) any DNA sequence or fragment

thereof that encodes the amino acid sequence that are set forth in SEQ ID NO:63 through to SEQ ID NO:123 using the universal genetic code or the codon usage of *C. albicans*; (c) any DNA sequence that hybridizes to the complement of the nucleotide sequences set forth in SEQ ID NO:1 through to SEQ ID NO:62 under stringent conditions, *e.g.*, hybridization to
5 filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65°C, or under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C, or under other hybridization conditions which are apparent to those of skill in the art (see, for example, Ausubel, F.M. *et al.*, eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing
10 Associates, Inc. and John Wiley & Sons, Inc., New York, at pp. 6.3.1-6.3.6 and 2.10.3). Preferably, the polynucleotides that hybridize to the complements of the DNA sequences disclosed herein encode gene products, *e.g.*, gene products that are functionally equivalent to a gene product encoded by a target gene. As described above, target gene sequences
15 include not only degenerate nucleotide sequences that encode the amino acid sequences of SEQ ID NO:63 to 123 in *C. albicans*, but also degenerate nucleotide sequences that when translated in organisms other than *C. Albicans*, would yield a polypeptide comprising one of the amino acid sequences of SEQ ID NO:63 to 123, or a fragment thereof. One of skill in the art would know how to select the appropriate codons or modify the nucleotide sequences
20 of SEQ ID NO: 1 to 62 when using the target gene sequences in *C. albicans* or in other organisms. Moreover, the term "target gene" encompasses genes that are naturally occurring in *Saccharomyces cerevisiae* or variants thereof, that share extensive nucleotide sequence homology with *C. albicans* genes having one of the DNA sequences that are set forth in SEQ ID NO:1 through to SEQ ID NO:62, *i.e.*, the orthologs in *S. cerevisiae*. It is
25 contemplated that methods for drug screening that can be applied to *C. albicans* genes can also be applied to orthologs of the same genes in the non-pathogenic *S. cerevisiae*.

In another embodiment, the invention also encompasses the following polynucleotides, host cells expressing such polynucleotides and the expression products of such nucleotides: (a) polynucleotides that encode portions of target gene product that
30 corresponds to its functional domains, and the polypeptide products encoded by such nucleotide sequences, and in which, in the case of receptor-type gene products, such domains include, but are not limited to signal sequences, extracellular domains (ECD), transmembrane domains (TM) and cytoplasmic domains (CD); (b) polynucleotides that encode mutants of a target gene product, in which all or part of one of its domains is deleted
35 or altered, and which, in the case of receptor-type gene products, such mutants include, but

are not limited to, mature proteins in which the signal sequence is cleaved, soluble receptors in which all or a portion of the TM is deleted, and nonfunctional receptors in which all or a portion of CD is deleted; and (d) polynucleotides that encode fusion proteins containing a target gene product or one of its domains fused to another polypeptide.

5 The invention also includes polynucleotides, preferably DNA molecules, that hybridize to, and are therefore the complements of, the DNA sequences of the target gene sequences. Such hybridization conditions can be highly stringent or less highly stringent, as described above and known in the art. The nucleic acid molecules of the invention that hybridize to the above described DNA sequences include oligodeoxynucleotides ("oligos")
10 which hybridize to the target gene under highly stringent or stringent conditions. In general, for oligos between 14 and 70 nucleotides in length the melting temperature (T_m) is calculated using the formula: $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log[\text{monovalent cations (molar)}]) + 0.41(\% \text{ G+C}) - (500/N)$

where N is the length of the probe. If the hybridization is carried out in a solution
15 containing formamide, the melting temperature may be calculated using the equation:
 $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log[\text{monovalent cations (molar)}]) + 0.41(\% \text{ G+C}) - (0.61)(\% \text{ formamide}) - (500/N)$.

where N is the length of the probe. In general, hybridization is carried out at about 20-25 degrees below T_m (for DNA-DNA hybrids) or about 10-15 degrees below T_m (for
20 RNA-DNA hybrids). Other exemplary highly stringent conditions may refer, *e.g.*, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). Examples of such oligos are set forth in SEQ ID NO:124-489.

These nucleic acid molecules can encode or act as target gene antisense
25 molecules, useful, for example, in target gene regulation and/or as antisense primers in amplification reactions of target gene nucleotide sequences. Further, such sequences can be used as part of ribozyme and/or triple helix sequences, also useful for target gene regulation. Still further, such molecules can be used as components of diagnostic methods whereby the presence of the pathogen can be detected. The uses of these nucleic acid molecules are
30 discussed in detail below.

Fragments of the target genes of the invention can be at least 10 nucleotides in length. In alternative embodiments, the fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 or more contiguous nucleotides in length. Alternatively, the fragments can comprise nucleotide
35 sequences that encode at least 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 350, 400, 450 or

more contiguous amino acid residues of the target gene products. Fragments of the target genes of the invention can also refer to exons or introns of the above described nucleic acid molecules, as well as portions of the coding regions of such nucleic acid molecules that encode functional domains such as signal sequences, extracellular domains (ECD),
5 transmembrane domains (TM) and cytoplasmic domains (CD).

5.4.2 Homologous Target Genes

In addition to the nucleotide sequences of *Candida albicans* described above, homologs or orthologs of these target gene sequences, as can be present in other species, can
10 be identified and isolated by molecular biological techniques well known in the art, and without undue experimentation, used in the methods of the invention. For example, homologous target genes in *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Phytophthora infestans*, *Puccinia seconditii*, *Pneumocystis carinii*, or any species falling within the genera
15 of any of the above species. Other yeasts in the genera of *Candida*, *Saccharomyces*, *Schizosaccharomyces*, *Sporobolomyces*, *Torulopsis*, *Trichosporon*, *Tricophyton*, *Dermatophytes*, *Microsporum*, *Wickerhamia*, *Ashbya*, *Blastomyces*, *Candida*, *Citeromyces*, *Crebrothecium*, *Cryptococcus*, *Debaryomyces*, *Endomycopsis*, *Geotrichum*, *Hansenula*, *Kloeckera*, *Kluveromyces*, *Lipomyces*, *Pichia*, *Rhodospiridium*, *Rhodotorula*, and *Yarrowia*
20 are also contemplated. Also included are homologs of these target gene sequences can be identified in and isolated from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*, *Trichosporon beigeli*,
25 *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Alternaria solanii*, *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Sclerotinia sclerotiorum*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, *Venturia inequalis*, *Verticillium dahliae* or any species
30 falling within the genera of any of the above species.

Accordingly, the present invention provides nucleotide sequences that are hybridizable to the polynucleotides of the target genes, and that are of a species other than *Saccharomyces cerevisiae* and *Candida albicans*. In one embodiment, the present invention encompasses an isolated nucleic acid comprising a nucleotide sequence that is at least 50% identical to a nucleotide sequence selected from the group consisting of SEQ ID No. 1
35 through to SEQ ID NO:62. In another embodiment, the present invention encompasses

an isolated nucleic acid comprising a nucleotide sequence that hybridizes under medium stringency conditions to a second nucleic acid that consists of a nucleotide sequence selected from the group consisting of SEQ ID NO:1 through to SEQ ID NO:62.

In yet another embodiment, the present invention includes an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide the amino acid sequence of which is at least 50% identical to an amino acid sequence selected from the group consisting of SEQ ID No.63 through to 123, wherein the polypeptide is that of a species other than *Saccharomyces cerevisiae* and *Candida albicans*.

Although the nucleotide sequences and amino acid sequences of homologs or orthologs of such genes in *S. cerevisiae* is mostly published, uses of such homologs or orthologs in *S. cerevisiae* in drug screening are not known and are thus specifically provided by the invention. To use such nucleotide and/or amino acid sequences of *S. cerevisiae*, public databases, such as Stanford Genomic Resources (www-genome.stanford.edu), Munich Information Centre for Protein Sequences (www.mips.biochem.mpg.de), or Proteome (www.proteome.com) may be used to identify and retrieve the sequences. In cases where the ortholog or homolog of a *C. albicans* gene in *S. cerevisiae* is known, the name of the *S. cerevisiae* gene is indicated in parenthesis in column 1 of Table I. Orthologs of *S. cerevisiae* can also be identified by hybridization assays using nucleic acid probes consisting of any one of the nucleotide sequences of SEQ ID NO: 1 to 61, and 490.

The nucleotide sequences of the invention still further include nucleotide sequences that have at least 40%, 45%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more nucleotide sequence identity to the nucleotide sequences set forth in SEQ ID NO:1 through to SEQ ID NO:62. The nucleotide sequences of the invention also include nucleotide sequences that encode polypeptides having at least 25%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or higher amino acid sequence identity or similarity to the amino acid sequences set forth in SEQ ID NO:63 through to 123.

To determine the percent identity of two amino acid sequences or of two nucleotide sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleotide sequence for optimal alignment with a second amino acid or nucleotide sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity =

number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences can also be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. U.S.A.* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.*, 1990, *J. Mol. Biol.* 215:403-0. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.*, for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the present invention. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.*, to score=50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule of the present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (see, *e.g.*, <http://www.ncbi.nlm.nih.gov>). Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

To isolate homologous target genes, the *C. albicans* target gene sequence described above can be labeled and used to screen a cDNA library constructed from mRNA obtained from the organism of interest. Hybridization conditions should be of a lower stringency when the cDNA library was derived from an organism different from the type of organism from which the labeled sequence was derived. cDNA screening can also identify clones derived from alternatively spliced transcripts in the same or different species. Alternatively, the labeled fragment can be used to screen a genomic library derived from the organism of interest, again, using appropriately stringent conditions. Low stringency conditions will be well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are

derived. For guidance regarding such conditions see, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, N.Y.; and Ausubel et al., 1989, Current Protocols in Molecular Biology, (Green Publishing Associates and Wiley Interscience, N.Y.).

5 Further, a homologous target gene sequence can be isolated by performing a polymerase chain reaction (PCR) using two degenerate oligonucleotide primer pools designed on the basis of amino acid sequences within the target gene of interest. The template for the reaction can be cDNA obtained by reverse transcription of mRNA prepared from the organism of interest. The PCR product can be subcloned and sequenced to ensure
10 that the amplified sequences represent the sequences of a homologous target gene sequence.

The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods well known to those of ordinary skill in the art. Alternatively, the labeled fragment can be used to screen a genomic library.

PCR technology can also be utilized to isolate full length cDNA sequences.
15 For example, RNA can be isolated, following standard procedures, from an organism of interest. A reverse transcription reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid can then be "tailed" with guanines using a standard terminal transferase reaction, the hybrid can be digested with RNAase H,
20 and second strand synthesis can then be primed with a poly-C primer. Thus, cDNA sequences upstream of the amplified fragment can easily be isolated. For a review of cloning strategies which can be used, see e.g., Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Springs Harbor Press, N.Y.; and Ausubel et al., 1989, Current Protocols in Molecular Biology, (Green Publishing Associates and Wiley Interscience,
25 N.Y.).

Additionally, an expression library can be constructed utilizing DNA isolated from or cDNA synthesized from the organism of interest. In this manner, gene products made by the homologous target gene can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against the *C. albicans* gene
30 product, as described, below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual," Cold Spring Harbor Press, Cold Spring Harbor). Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis by well known methods.

Alternatively, homologous target genes or polypeptides may be identified by
35 searching a database to identify sequences having a desired level of homology to a target

gene or polypeptide involved in proliferation, virulence or pathogenicity. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In various embodiments, the databases are screened to identify nucleic acids with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, or at least 40% identity to a target nucleotide sequence, or a portion thereof. In other embodiments, the databases are screened to identify polypeptides having at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% identity or similarity to a polypeptide involved in proliferation, virulence or pathogenicity or a portion thereof.

Alternatively, functionally homologous target sequences or polypeptides may be identified by creating mutations that have phenotypes by removing or altering the function of a gene. This can be done for one or all genes in a given fungal species including, for example: *Saccharomyces cerevisiae*, *Candida albicans*, and *Aspergillus fumigatus*. Having mutants in the genes of one fungal species offers a method to identify functionally similar genes (orthologs) or related genes (paralogs) in another species, by use of a functional complementation test.

A library of gene or cDNA copies of messenger RNA of genes can be made from a given species, e.g. *Candida albicans*, and the library cloned into a vector permitting expression (for example, with the *Candida albicans* promoters or a *Saccharomyces cerevisiae* promoter) of the genes in a second species, e.g. *Saccharomyces cerevisiae*. Such a library is referred to as a "heterologous library." Transformation of the *Candida albicans* heterologous library into a defined mutant of *Saccharomyces cerevisiae* that is functionally deficient with respect to the identified gene, and screening or selecting for a gene in the heterologous library that restores phenotypic function in whole or in part of the mutational defect is said to be "heterologous functional complementation" and in this example, permits identification of gene in *Candida albicans* that are functionally related to the mutated gene in *Saccharomyces cerevisiae*. Inherent in this functional-complementation method, is the ability to restore gene function without the requirement for sequence similarity of nucleic acids or polypeptides; that is, this method permits interspecific identification of genes with conserved biological function, even where sequence similarity comparisons fail to reveal or suggest such conservation.

In those instances in which the gene to be tested is an essential gene, a number of possibilities exist regarding performing heterologous functional complementation tests. The mutation in the essential gene can be a conditional allele, including but not limited to, a temperature-sensitive allele, an allele conditionally expressed from a regulatable promoter, or an allele that has been rendered the mRNA transcript or the encoded gene product conditionally unstable. Alternatively, the strain carrying a mutation in an essential gene can be propagated

using a copy of the native gene (a wild type copy of the gene mutated from the same species) on a vector comprising a marker that can be selected against, permitting selection for those strains carrying few or no copies of the vector and the included wild type allele. A strain constructed in this manner is transformed with the heterologous library, and those clones in which a
5 heterologous gene can functionally complement the essential gene mutation, are selected on medium non-permissive for maintenance of the plasmid carrying the wild type gene.

In the following example, the identification, by functional complementation, of a *Candida albicans* homolog of a *Saccharomyces cerevisiae* gene, *KRE 9*, is described. (Lussier *et al.* 1998, "The *Candida albicans* *KRE 9* gene is required for cell wall β -1,6-glucan synthesis and
10 is essential for growth on glucose," *Proc. Natl. Acad. Sci. USA* 95: 9825-30). The host strain was a *Saccharomyces cerevisiae* haploid null mutant in *KRE 9*, *kre 9::HIS3*, which has a severe growth defect phenotype. The host strain carried a wild type copy of the native *Saccharomyces cerevisiae* *KRE 9* gene on a LYS-2 based pRS317 shuttle vector and was transformed with a
15 *Candida albicans* genomic library. This heterologous library was constructed using, as a vector, the multicopy plasmid YEp352, which carries the *URA3* gene as a selectable marker. To screen for plasmids supporting growth of the *kre 9::HIS 3* mutant host, approximately 20,000 colonies capable of growth in the absence of histidine, lysine, and uracil, were replica-plated onto minimal medium containing α -amino adipate as a nitrogen source to allow selection for cells
20 that have lost the LYS2 plasmid-based copy of *KRE 9* and that possess a copy of a functionally-complementing *Candida albicans* ortholog, Ca*KRE 9*. These cells were tested further for loss of the pRS317-*KRE 9* plasmid by their inability to grow in the absence of lysine, and YEp352-based *Candida albicans* genomic DNA was recovered from them. On
25 retransformation of the *Saccharomyces cerevisiae* *kre 9::HIS3* mutant, a specific genomic insert of 8kb of *Candida albicans* was recovered that was able to restore growth partially. Following further subcloning using functional complementation for selection, a 1.6 kb DNA fragment was obtained that contained the functional *Candida albicans* *KRE 9* gene.

A heterologous functional complementation test is not restricted to the exchange of genetic information between *Candida albicans* and *Saccharomyces cerevisiae*; functional
30 complementation tests can be performed, as described above, using any pair of fungal species. For example, the *CRE1* gene of the fungus *Sclerotinia sclerotiorum* can functionally complement the *creAD30* mutant of the *CREA* gene of *Aspergillus nidulans* (see Vautard *et al.* 1999, "The glucose repressor gene *CRE1* from *Sclerotinia sclerotiorum* is functionally related to *CREA* from *Aspergillus nidulans* but not to the Mig proteins from *Saccharomyces*
35 *cerevisiae*," *FEBS Lett.* 453: 54-58).

In yet another embodiment, where the source of nucleic acid deposited on a gene

expression array and the source of the nucleic acid probe being hybridized to the array are from two different species of organisms, the results allow rapid identification of homologous genes in the two species.

In yet another embodiment, the invention also encompasses (a) DNA vectors
5 that contain a nucleotide sequence comprising any of the foregoing coding sequences of the target gene and/or their complements (including antisense); (b) DNA expression vectors that contain a nucleotide sequence comprising any of the foregoing coding sequences operably linked with a regulatory element that directs the expression of the coding sequences; and (c) genetically engineered host cells that contain any of the foregoing coding sequences of the target gene
10 operably linked with a regulatory element that directs the expression of the coding sequences in the host cell. Vectors, expression constructs, expression vectors, and genetically engineered host cells containing the coding sequences of homologous target genes of other species (excluding *S. cerevisiae*) are also contemplated. Also contemplated are genetically engineered host cells containing mutant alleles in homologous target genes of the other species. As used herein,
15 regulatory elements include but are not limited to inducible and non-inducible promoters, enhancers; operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include but are not limited to the *lac* system, the *trp* system, the tet system and other antibiotic-based repression systems (e.g. PIP), the *TAC* system, the TRC system, the major operator and promoter regions of phage A, the control regions of fd coat protein, and the fungal promoters for 3-phosphoglycerate kinase, acid phosphatase, the yeast
20 mating pheromone responsive promoters (e.g. STE2 and STE3), and promoters isolated from genes involved in carbohydrate metabolism (e.g. GAL promoters), phosphate-responsive promoters (e.g. PHO5), or amino acid metabolism (e.g. MET genes). The invention includes fragments of any of the DNA vector sequences disclosed herein.

25 A variety of techniques can be utilized to further characterize the identified essential genes and virulence genes. First, the nucleotide sequence of the identified genes can be used to reveal homologies to one or more known sequence motifs which can yield information regarding the biological function of the identified gene product. Computer programs well known in the art can be employed to identify such relationships. Second, the sequences of the
30 identified genes can be used, utilizing standard techniques such as in situ hybridization, to place the genes onto chromosome maps and genetic maps which can be correlated with similar maps constructed for another organism, e.g., *Saccharomyces cerevisiae*. The information obtained through such characterizations can suggest relevant methods for using the polynucleotides and polypeptides for discovery of drugs against *Candida albicans* and other pathogens.

35 Methods for performing the uses listed above are well known to those skilled in

the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual," 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques," Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987. Many of the uses of the polynucleotides and polypeptides of the identified essential genes are discussed in details hereinbelow.

5.4.3 Target Gene Products

The target gene products used and encompassed in the methods and compositions of the present invention include those gene products (*e.g.*, RNA or proteins) that are encoded by the target essential gene sequences as described above, such as, the target gene sequences set forth in SEQ ID NO:1 through to 62. In Table II, the amino acid sequences of SEQ ID NO: 63 to 123 are deduced using the codon usage of *C. albicans* from the respective nucleotide sequences of SEQ ID NO: 1 to 61. However, when expressed in an organism other than *C. albicans*, protein products of the target genes having the amino acid sequences of SEQ ID NO: 63 to 123 may be encoded by nucleotide sequences that are translated using the universal genetic code. One of skill in the art would know the modifications that are necessary to accommodate for such a difference in codon usage.

In addition, however, the methods and compositions of the invention also use and encompass proteins and polypeptides that represent functionally equivalent gene products. Such functionally equivalent gene products include, but are not limited to, natural variants of the polypeptides having an amino acid sequence set forth in SEQ ID NO:63 through to 123.

Such equivalent target gene products can contain, *e.g.*, deletions, additions or substitutions of amino acid residues within the amino acid sequences encoded by the target gene sequences described above, but which result in a silent change, thus producing a functionally equivalent target gene product. Amino acid substitutions can be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues involved. For example, nonpolar (*i.e.*, hydrophobic) amino acid residues can include alanine (Ala or A), leucine (Leu or L), isoleucine (Ile or I), valine (Val or V), proline (Pro or P), phenylalanine (Phe or F), tryptophan (Trp or W) and methionine (Met or M); polar neutral amino acid residues can include glycine (Gly or G), serine (Ser or S), threonine (Thr or T), cysteine (Cys or C), tyrosine (Tyr or Y), asparagine (Asn or N) and glutamine (Gln or Q); positively charged (*i.e.*, basic) amino acid residues can include arginine (Arg or R), lysine (Lys or K) and histidine (His or H); and negatively charged (*i.e.*, acidic) amino acid residues can include aspartic acid (Asp or D) and glutamic acid (Glu or E).

In one particular embodiment, a composition comprising a mixture of natural variants of the polypeptides having one of SEQ ID NO:63 through to 123 is provided. Since it is known in the art that, in *C. albicans*, 99% of the tRNA molecules that recognize the codon CTG is charged with a serine residue, and 1% are charged with a leucine residue, there is a possibility that during biosynthesis, a leucine is incorporated into a growing polypeptide chain. Accordingly, when a nucleotide sequence comprising the codon CTG is translated in *C. albicans*, a small percentage of the resulting polypeptides may have a leucine residue in positions where a serine residue encoded by CTG (conforming to the codon usage of *C. albicans*) is expected. The product of translation of such a nucleotide sequence may comprise a mixture of polypeptides with minor leucine/serine variations at positions that correspond to a CTG codon in the nucleotide sequence.

"Functionally equivalent," as the term is utilized herein, refers to a polypeptide capable of exhibiting a substantially similar *in vivo* activity as the *Candida albicans* target gene product encoded by one or more of the target gene sequences described in Table II. Alternatively, when utilized as part of assays described hereinbelow, the term "functionally equivalent" can refer to peptides or polypeptides that are capable of interacting with other cellular or extracellular molecules in a manner substantially similar to the way in which the corresponding portion of the target gene product would interact with such other molecules. Preferably, the functionally equivalent target gene products of the invention are also the same size or about the same size as a target gene product encoded by one or more of the target gene sequences described in Table II.

In another embodiment of the invention, the use of target gene products that are RNA or proteins of *Saccharomyces cerevisiae* are provided.

Peptides and polypeptides corresponding to one or more domains of the target gene products (*e.g.*, signal sequence, TM, ECD, CD, or ligand-binding domains), truncated or deleted target gene products (*e.g.*, polypeptides in which one or more domains of a target gene product are deleted) and fusion target gene proteins (*e.g.*, proteins in which a full length or truncated or deleted target gene product, or a peptide or polypeptide corresponding to one or more domains of a target gene product is fused to an unrelated protein) are also within the scope of the present invention. Such peptides and polypeptides (also referred to as chimeric protein or polypeptides) can be readily designed by those skilled in the art on the basis of the target gene nucleotide and amino acid sequences listed in Table II. Exemplary fusion proteins can include, but are not limited to, epitope tag-fusion proteins which facilitates isolation of the target gene product by affinity chromatography using reagents that binds the epitope. Other exemplary fusion proteins include fusions to any amino acid sequence that allows, *e.g.*, the fusion protein to

be anchored to a cell membrane, thereby allowing target gene polypeptides to be exhibited on a cell surface; or fusions to an enzyme (e.g., β -galactosidase encoded by the LAC4 gene of *Kluyveromyces lactis* (Leuker et al., 1994, Mol. Gen. Genet., 245:212-217)), to a fluorescent protein (e.g., from *Renilla reniformis* (Srikantha et al., 1996, J. Bacteriol. 178:121-129), or to a luminescent protein which can provide a marker function. Accordingly, the invention provides a fusion protein comprising a fragment of a first polypeptide fused to a second polypeptide, said fragment of the first polypeptide consisting of at least 6 consecutive residues of an amino acid sequence selected from one of SEQ ID NO: 63 to 123.

Other modifications of the target gene product coding sequences described above can be made to generate polypeptides that are better suited, e.g., for expression, for scale up, etc. in a chosen host cell. For example, cysteine residues can be deleted or substituted with another amino acid in order to eliminate disulfide bridges.

The target gene products of the invention preferably comprise at least as many contiguous amino acid residues as are necessary to represent an epitope fragment (that is, for the gene products to be recognized by an antibody directed to the target gene product). For example, such protein fragments or peptides can comprise at least about 8 contiguous amino acid residues from a full length differentially expressed or pathway gene product. In alternative embodiments, the protein fragments and peptides of the invention can comprise about 6, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450 or more contiguous amino acid residues of a target gene product.

The target gene products used and encompassed in the methods and compositions of the present invention also encompass amino acid sequences encoded by one or more of the above-described target gene sequences of the invention wherein domains often encoded by one or more exons of those sequences, or fragments thereof, have been deleted. The target gene products of the invention can still further comprise post translational modifications, including, but not limited to, glycosylations, acetylations and myristylations.

The target gene products of the invention can be readily produced, e.g., by synthetic techniques or by methods of recombinant DNA technology using techniques that are well known in the art. Thus, methods for preparing the target gene products of the invention are discussed herein. First, the polypeptides and peptides of the invention can be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman and Co., N.Y., which is incorporated herein by reference in its entirety. Peptides can, for example, be synthesized on a solid support or in solution.

Alternatively, recombinant DNA methods which are well known to those skilled

in the art can be used to construct expression vectors containing target gene protein coding sequences such as those set forth in SEQ ID NO: 1 through to 61, and appropriate transcriptional/translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* recombination/genetic
5 recombination. See, for example, the techniques described in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., Pla et al., Yeast 12:1677-1702 (1996), which are incorporated by reference herein in their entireties, and Ausubel, 1989, *supra*. Alternatively, RNA capable of encoding target gene protein sequences can be chemically synthesized using, for example, synthesizers. See, for example, the
10 techniques described in *Oligonucleotide Synthesis*, 1984, Gait, M.J. ed., IRL Press, Oxford, which is incorporated by reference herein in its entirety.

A variety of host-expression vector systems can be utilized to express the target gene coding sequences of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest can be produced and subsequently purified, but also
15 represent cells which can, when transformed or transfected with the appropriate nucleotide coding sequences, exhibit the target gene protein of the invention *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing target gene protein coding sequences; yeast (*e.g.*, *Saccharomyces*, *Schizosaccharomyces*,
20 *Neurospora*, *Aspergillus*, *Candida*, *Pichia*) transformed with recombinant yeast expression vectors containing the target gene protein coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing the target gene protein coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant
25 plasmid expression vectors (*e.g.*, Ti plasmid) containing target gene protein coding sequences; or mammalian cell systems (*e.g.* COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). If necessary, the nucleotide sequences of coding regions may be
30 modified according to the codon usage of the host such that the translated product has the correct amino acid sequence.

In bacterial systems, a number of expression vectors can be advantageously selected depending upon the use intended for the target gene protein being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of
35 antibodies or to screen peptide libraries, for example, vectors which direct the expression of high

levels of fusion protein products that are readily purified can be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., 1983, *EMBO J.* 2:1791), in which the target gene protein coding sequence can be ligated individually into the vector in frame with the lacZ coding region so that a fusion protein is produced; pIN vectors
5 (Inouye & Inouye, 1985, *Nucleic Acids Res.* 13:3101-3109; Van Heeke & Schuster, 1989, *J. Biol. Chem.* 264:5503-5509); and the like. pGEX vectors can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are
10 designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene protein can be released from the GST moiety.

When a target gene is to be expressed in mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the target gene coding sequence of interest can be ligated to an adenovirus
15 transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene can then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing target gene protein in infected hosts, (e.g., See Logan & Shenk, 1984, *Proc. Natl. Acad. Sci. USA* 81:3655-3659).
20 Specific initiation signals can also be required for efficient translation of inserted target gene coding sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire target gene, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals can be needed. However, in cases where only a portion of the target gene coding sequence is inserted,
25 exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of appropriate transcription
30 enhancer elements, transcription terminators, etc. (see Bittner et al., 1987, *Methods in Enzymol.* 153:516-544).

In addition, a host cell strain can be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein
35 products can be important for the function of the protein. Different host cells have characteristic

and specific mechanisms for the post-translational processing and modification of proteins.

Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and

5 phosphorylation of the gene product can be used.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the target gene protein can be engineered. Host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, *etc.*), and a selectable marker. Following the introduction of the foreign DNA, engineered cells can be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method can

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15 advantageously be used to engineer cell lines which express the target gene protein. Such engineered cell lines can be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the target gene protein.

A number of selection systems can be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., 1977, *Cell* 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, *Proc. Natl. Acad. Sci. USA* 48:2026), and adenine phosphoribosyltransferase (Lowy et al., 1980, *Cell* 22:817) genes can be employed in tk⁻, hgp⁺ or apr⁺ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for dhfr, which confers resistance to methotrexate (Wigler et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:3567; O'Hare et al., 1981, *Proc. Natl. Acad. Sci. USA* 78:1527); gpt, which

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25 confers resistance to mycophenolic acid (Mulligan & Berg, 1981, *Proc. Natl. Acad. Sci. USA* 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin et al., 1981, *J. Mol. Biol.* 150:1); and hyg⁺, which confers resistance to hygromycin (Santerre et al., 1984, *Gene* 30:147) genes.

Alternatively, any fusion protein may be readily purified by utilizing an antibody

30 specific for the fusion protein being expressed. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cells lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88: 8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine

35 residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto

Ni²⁺-nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers. Fusions at the carboxy terminal of the target gene product are also contemplated.

When used as a component in assay systems such as those described herein, the target gene protein can be labeled, either directly or indirectly, to facilitate detection of a complex formed between the target gene protein and a test substance. Any of a variety of suitable labeling systems can be used including but not limited to radioisotopes such as ¹²⁵I; enzyme labeling systems that generate a detectable colorimetric signal or light when exposed to substrate; and fluorescent labels.

Indirect labeling involves the use of a protein, such as a labeled antibody, which specifically binds to either a target gene product. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

Following expression of the target gene protein encoded by the identified target nucleotide sequence, the protein is purified. Protein purification techniques are well known in the art. Proteins encoded and expressed from identified exogenous nucleotide sequence¹⁷ s can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Alternatively, epitope tagging of the protein can be used to allow simple one step purification of the protein. In addition, chromatographic methods such as ion-exchange chromatography, gel filtration, use of hydroxyapatite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography, may also be used to purify the protein. Electrophoretic methods such as one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis, isoelectric focusing, and others are contemplated as purification methods. Also, affinity chromatographic methods, comprising solid phase bound- antibody, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

In addition, the purified target gene products, fragments thereof, or derivatives thereof may be administered to an individual in a pharmaceutically acceptable carrier to induce an immune response against the protein or polypeptide. Preferably, the immune response is a protective immune response which protects the individual. Methods for determining appropriate dosages of the protein (including use of adjuvants) and pharmaceutically acceptable carriers are familiar to those skilled in the art.

5.4.4 Antibodies Specific for Target Gene Products

Described herein are methods for the production of antibodies capable of specifically recognizing epitopes of one or more of the target gene products described above. Such antibodies can include, but are not limited to, polyclonal antibodies, monoclonal antibodies
5 (mAbs), human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

For the production of antibodies to a target gene or gene product, various host animals can be immunized by injection with a target gene protein, or a portion thereof. Such
10 host animals can include but are not limited to rabbits, mice, and rats, to name but a few. Various adjuvants can be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol, and potentially
15 useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Accordingly, the invention provides a method of eliciting an immune response in an animal, comprising introducing into the animal an immunogenic composition comprising an isolated polypeptide, the amino acid sequence of which comprises at least 6 consecutive residues of one of SEQ ID NO: 63 to 123.

20 Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen, such as target gene product, or an antigenic functional derivative thereof. For the production of polyclonal antibodies, host animals such as those described above, can be immunized by injection with differentially expressed or pathway gene product supplemented with adjuvants as also described above. The
25 antibody titer in the immunized animal can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be isolated from the animal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

30 Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to the hybridoma technique of Kohler and Milstein, (1975, *Nature* 256:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor et al., 1983, *Immunology Today*
35 4:72; Cole et al., 1983, *Proc. Natl. Acad. Sci. USA* 80:2026-2030), and the EBV-hybridoma

technique (Cole et al., 1985, *Monoclonal Antibodies And Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96). Such antibodies can be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention can be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs *in vivo* makes this the presently preferred method of production.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) *Science* 240:1041-1043; Liu et al. (1987) *Proc. Natl.*

Acad. Sci. USA 84:3439-3443; Liu et al. (1987) *J. Immunol.* 139:3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al. (1987) *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi et al. (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al. (1986) *Nature* 321:552-525; Verhoeyan et al. (1988) *Science* 239:1534; and Beidler et al. (1988) *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al. (1994) *Bio/technology* 12:899-903).

Antibody fragments which recognize specific epitopes can be generated by known techniques. For example, such fragments include but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries can be constructed (Huse et al., 1989, *Science* 246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies of the present invention may also be described or specified in terms of their binding affinity to a target gene product. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5

10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

Antibodies directed against a target gene product or fragment thereof can be used to detect the a target gene product in order to evaluate the abundance and pattern of expression of the polypeptide under various environmental conditions, in different morphological forms (mycelium, yeast, spores) and stages of an organism's life cycle. Antibodies directed against a target gene product or fragment thereof can be used diagnostically to monitor levels of a target gene product in the tissue of an infected host as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen.

Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

Further, antibodies directed against a target gene product or fragment thereof can be used therapeutically to treat an infectious disease by preventing infection, and/or inhibiting growth of the pathogen. Antibodies can also be used to modify a biological activity of a target gene product. Antibodies to gene products related to virulence or pathogenicity can also be used to prevent infection and alleviate one or more symptoms associated with infection by the organism. To facilitate or enhance its therapeutic effect, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a toxin or fungicidal agent. Techniques for conjugating a therapeutic moiety to antibodies are well known, see, *e.g.*, Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

An antibody with or without a therapeutic moiety conjugated to it can be used as a therapeutic that is administered alone or in combination with chemotherapeutic agents.

5.4.5 Antisense Molecules

The use of antisense molecules as inhibitors of gene expression may be a specific, genetically based therapeutic approach (for a review, see Stein, in Ch. 69, Section 5 "Cancer: Principle and Practice of Oncology", 4th ed., ed. by DeVita et al., J.B. Lippincott, Philadelphia 1993). The present invention provides the therapeutic or prophylactic use of nucleic acids of at least six nucleotides that are antisense to a target essential or virulence gene or a portion thereof. An "antisense" target nucleic acid as used herein refers to a nucleic acid capable of hybridizing to a portion of a target gene RNA (preferably mRNA) by virtue of some sequence complementarity. The invention further provides pharmaceutical compositions comprising an effective amount of the antisense nucleic acids of the invention in a pharmaceutically acceptable carrier, as described *infra*.

In another embodiment, the invention is directed to methods for inhibiting the expression of a target gene in an organism of interest, such as *C. albicans* *in vitro* or *in vivo* comprising providing the cell with an effective amount of a composition comprising an antisense nucleic acid of the invention. Multiple antisense polynucleotides hybridizable to different target genes may be used in combinations, sequentially or simultaneously.

In another embodiment, the present invention is directed toward methods for modulating expression of an essential gene which has been identified by the methods described *supra*, in which an antisense RNA molecule, which inhibits translation of mRNA transcribed from an essential gene, is expressed from a regulatable promoter. In one aspect of this embodiment, the antisense RNA molecule is expressed in a GRACE strain of *Candida albicans* or another GRACE strain constructed from another diploid pathogenic organism. In other aspects of this embodiment, the antisense RNA molecule is expressed in a wild-type or other non-GRACE strain of *Candida albicans* or another diploid pathogenic organism, including animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*, *Trichosporon beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydiss*, or any species falling within the genera of any of the above species.

The nucleic acid molecule comprising an antisense nucleotide sequence of the invention may be complementary to a coding and/or noncoding region of a target gene mRNA. The antisense molecules will bind to the complementary target gene mRNA transcripts and

reduce or prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA
5 may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Nucleic acid molecules that are complementary to the 5' end of the message, e.g.,
10 the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have recently been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335.

Nucleic acid molecules comprising nucleotide sequences complementary to the
15 5' untranslated region of the mRNA can include the complement of the AUG start codon. Antisense nucleic acid molecules complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5', 3'- or coding region of target gene mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about
20 50 nucleotides in length. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides, at least 50 nucleotides, or at least 200 nucleotides.

Regardless of the choice of target gene sequence, it is preferred that in vitro studies are first performed to quantitate the ability of the antisense molecule to inhibit gene expression. It is preferred that these studies utilize controls that distinguish between antisense
25 gene inhibition and nonspecific biological effects of oligonucleotides. It is also preferred that these studies compare levels of the target RNA or protein with that of an internal control RNA or protein. Additionally, it is envisioned that results obtained using the antisense oligonucleotide are compared with those obtained using a control oligonucleotide. It is preferred that the control oligonucleotide is of approximately the same length as the test oligonucleotide and that the
30 nucleotide sequence of the oligonucleotide differs from the antisense sequence no more than is necessary to prevent specific hybridization to the target sequence.

The antisense molecule can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The antisense molecule can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve
35 stability of the molecule, hybridization, etc. The antisense molecule may include other

appended groups such as peptides (e.g., for targeting cell receptors *in vivo*), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, *BioTechniques* 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the antisense molecule may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense molecule may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense molecule may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense molecule comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense molecule is an α -anomeric oligonucleotide. An α -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gautier et al., 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, *Nucl. Acids Res.* 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, *FEBS Lett.* 215:327-330).

Antisense molecules of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, *Nucl. Acids Res.*

16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region of a target gene could be used, those complementary to the transcribed untranslated region are also preferred.

5 Pharmaceutical compositions of the invention comprising an effective amount of an antisense nucleic acid in a pharmaceutically acceptable carrier, can be administered to a subject infected with the pathogen of interest.

The amount of antisense nucleic acid which will be effective in the treatment of a particular disease caused by the pathogen will depend on the site of the infection or condition, and can be determined by standard techniques. Where possible, it is desirable to determine the antisense cytotoxicity of the pathogen to be treated in vitro, and then in useful animal model systems prior to testing and use in humans.

A number of methods have been developed for delivering antisense DNA or RNA to cells; e.g., antisense molecules can be injected directly into the tissue site in which the pathogens are residing, or modified antisense molecules, designed to target the desired cells (e.g., antisense molecule linked to peptides or antibodies that specifically bind receptors or antigens expressed on the pathogen's cell surface) can be administered systemically. Antisense molecules can be delivered to the desired cell population via a delivery complex. In a specific embodiment, pharmaceutical compositions comprising antisense nucleic acids of the target genes are administered via biopolymers (e.g., poly- β -1-4-N-acetylglucosamine polysaccharide), liposomes, microparticles, or microcapsules. In various embodiments of the invention, it may be useful to use such compositions to achieve sustained release of the antisense nucleic acids. In a specific embodiment, it may be desirable to utilize liposomes targeted via antibodies to specific identifiable pathogen antigens (Leonetti et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2448-2451; Renneisen et al., 1990, J. Biol. Chem. 265:16337-16342).

5.4.6 Ribozyme Molecules

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA (For a review see, for example Rossi, J., 1994, Current Biology 4:469-471). The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage. The composition of ribozyme molecules must include one or more sequences complementary to the target gene mRNA, and must include the well known catalytic sequence responsible for mRNA cleavage. For this sequence, see U.S. Pat. No. 5,093,246, which is incorporated by reference herein in its entirety. As such, within the scope of the invention are engineered hammerhead

motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences encoding target gene proteins.

Ribozyme molecules designed to catalytically cleave specific target gene mRNA transcripts can also be used to prevent translation of target gene mRNA and expression of target genes. While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target gene mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, 1988, *Nature*, 334:585-591. Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug, et al., 1984, *Science*, 224:574-578; Zaug and Cech, 1986, *Science*, 231:470-475; Zaug, et al., 1986, *Nature*, 324:429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, *Cell*, 47:207-216). The Cech-type ribozymes have an eight base pair active site which hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes which target eight base-pair active site sequences that are present in a target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the target gene in vivo. Because ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency. Multiple ribozyme molecules directed against different target genes can also be used in combinations, sequentially or simultaneously.

Anti-sense RNA and DNA, ribozyme, and triple helix molecules of the invention can be prepared by any method known in the art for the synthesis of DNA and RNA molecules. These include techniques for chemically synthesizing oligodeoxyribonucleotides and oligoribonucleotides well known in the art such as for example solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules can be generated by in vitro and in vivo transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences

can be incorporated into a wide variety of vectors which incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines. These nucleic acid constructs can be administered
5 selectively to the desired cell population via a delivery complex.

Various well-known modifications to the DNA molecules can be introduced as a means of increasing intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences of ribo- or deoxy- nucleotides to the 5' and/or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phospho-
10 diesterase linkages within the oligodeoxyribonucleotide backbone.

5.5 SCREENING ASSAYS

The following assays are designed to identify compounds that bind to target gene products, bind to other cellular proteins that interact with the target gene product, and to
15 compounds that interfere with the interaction of the target gene product with other cellular proteins. Compounds identified via such methods can include compounds which modulate the activity of a polypeptide encoded by a target gene of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds which modulate the expression
20 of the polynucleotide (that is, increase or decrease expression relative to expression levels observed in the absence of the compound), or increase or decrease the stability of the expressed product encoded by that polynucleotide. Compounds, such as compounds identified via the methods of the invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

25 Accordingly, the present invention provides a method for identifying an antimycotic compound comprising screening a plurality of compounds to identify a compound that modulates the activity or level of a gene product, said gene product being encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 to 61, or a nucleotide sequence that is naturally occurring in *Saccharomyces cerevisiae* and that is the ortholog of a
30 gene having a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 to 61.

5.5.1 In Vitro Screening Assays

In vitro systems are designed to identify compounds capable of binding the target gene products of the invention. Compounds identified in this manner are useful, for example, in
35 modulating the activity of wild type and/or mutant target gene products, are useful in elucidating

the biological function of target gene products, are utilized in screens for identifying other compounds that disrupt normal target gene product interactions, or are useful themselves for the disruption of such interactions.

5 The principle of the assays used to identify compounds that bind to the target gene product involves preparing a reaction mixture comprising the target gene product and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex which is removed and/or detected within the reaction mixture. These assays are conducted in a variety of ways. For example, one method involves anchoring target gene product or the test substance onto a solid phase and detecting target gene product/test
10 compound complexes anchored, *via* the intermolecular binding reaction, to the solid phase at the end of the reaction. In one embodiment of such a method, the target gene product is anchored onto a solid surface, and the test compound, which is not anchored, is labeled, either directly or indirectly.

In practice, microtiter plates are conveniently utilized as the solid phase. The
15 anchored component is immobilized by non-covalent or covalent attachments. Non-covalent attachment can be accomplished by simply coating the solid surface with a solution of the protein and drying the coated surface. Alternatively, an immobilized antibody, preferably a monoclonal antibody, specific for the protein to be immobilized is used to anchor the protein to the solid surface. The surfaces are prepared in advance and stored.

20 In order to conduct the assay, the nonimmobilized component is added to the coated surface containing the anchored component. After the reaction is complete, unreacted components are removed (*e. g.*, by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface is accomplished in a number of ways. Where the previously nonimmobilized
25 component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the previously nonimmobilized component is not pre-labeled, an indirect label is used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the previously nonimmobilized component (the antibody, in turn, is directly labeled or indirectly labeled with a labeled anti-Ig antibody).

30 Alternatively, a reaction is conducted in a liquid phase, the reaction products are separated from unreacted components, and complexes are detected; *e.g.*, using an immobilized antibody specific for the target gene product or for the test compound, to anchor complexes formed in solution, and a second labeled antibody, specific for the other component of the complex to allow detection of anchored complexes.

35

5.5.1.1 Assays For Proteins That Interact With A Target Gene Product

Any method suitable for detecting protein-protein interactions can be employed for identifying novel target protein-cellular or extracellular protein interactions.

The target gene products of the invention interact, in vivo, with one or more
5 cellular or extracellular macromolecules, such as proteins. Such macromolecules include, but are not limited to, nucleic acid molecules and proteins identified via methods such as those described above. For purposes of this discussion, such cellular and extracellular macromolecules are referred to herein as "binding partners." Compounds that disrupt such interactions can be useful in regulating the activity of the target gene protein, especially mutant
10 target gene proteins. Such compounds include, but are not limited to molecules such as antibodies, peptides, and the like, as described.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the target gene product and its cellular or extracellular binding partner or partners involves preparing a reaction mixture containing the target gene
15 product and the binding partner under conditions and for a time sufficient to allow the two to interact and bind, thus forming a complex. In order to test a compound for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound is initially included in the reaction mixture, or added at a time subsequent to the addition of target gene product and its cellular or extracellular binding partner. Control-reaction
20 mixtures are incubated without the test compound. The formation of complexes between the target gene protein and the cellular or extracellular binding partner is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the target gene protein and the interactive binding partner. Additionally, complex formation within reaction mixtures
25 containing the test compound and normal target gene protein can also be compared to complex formation within reaction mixtures containing the test compound and a mutant target gene protein. This comparison can be important in those cases wherein it is desirable to identify compounds that disrupt intermolecular interactions involving mutant but not normal target gene proteins.

30 The assay for compounds that interfere with the interaction of the target gene products and binding partners is conducted in either a heterogeneous or a homogeneous format. Heterogeneous assays involve anchoring either the target gene product or the binding partner onto a solid phase and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either
35 approach, the order of addition of reactants is varied to obtain different information about the

compounds being tested. For example, test compounds that interfere with the interaction between the target gene products and the binding partners, *e.g.*, by competition, are identified by conducting the reaction in the presence of the test substance; *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the target gene protein and an interacting
5 cellular or extracellular binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, are tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are described briefly below.

In a heterogeneous assay system, either the target gene protein or the interactive
10 cellular or extracellular binding partner, is anchored onto a solid surface, while the non-anchored species is labeled, either directly or indirectly. In practice, microtiter plates are conveniently utilized. The anchored species is immobilized either by non-covalent or covalent attachment. Non-covalent attachment is accomplished simply by coating the solid surface with a solution of the target gene product or binding partner and drying the coated surface. Alternatively, an
15 immobilized antibody specific for the species to be anchored is used to anchor the species to the solid surface. The surfaces can be prepared in advance and stored.

In order to conduct the assay, the partner of the immobilized species is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted components are removed (*e.g.*, by washing) and any complexes formed will remain
20 immobilized on the solid surface. The detection of complexes anchored on the solid surface is accomplished in a number of ways. Where the non-immobilized species is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized species is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the initially non-immobilized
25 species (the antibody, in turn, is directly labeled or indirectly labeled with a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which inhibit complex formation or which disrupt preformed complexes are detected.

Alternatively, the reaction is conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from unreacted components, and
30 complexes detected; *e.g.*, using an immobilized antibody specific for one of the binding components to anchor any complexes formed in solution, and a second, labeled antibody specific for the other partner to detect anchored complexes. Again, depending upon the order of addition of reactants to the liquid phase, test compounds which inhibit complex or which disrupt preformed complexes are identified.

35 In an alternate embodiment of the invention, a homogeneous assay can be used.

In this approach, a preformed complex of the target gene protein and the interacting cellular or extracellular binding partner is prepared in which either the target gene product or its binding partner is labeled, but the signal generated by the label is quenched due to complex formation (see, e.g., U.S. Patent No. 4,109,496 by Rubenstein which utilizes this approach for immunoassays). The addition of a test substance that competes with and displaces one of the species from the preformed complex results in the generation of a signal above background. In this way, test substances which disrupt target gene protein/cellular or extracellular binding partner interaction are identified.

In a particular embodiment, the target gene product is prepared for immobilization using recombinant DNA techniques described above. For example, the target gene coding region is fused to a glutathione-S-transferase (GST) gene using a fusion vector, such as pGEX-5X-1, in such a manner that its binding activity is maintained in the resulting fusion protein. The interactive cellular or extracellular binding partner is purified and used to raise a monoclonal antibody, using methods routinely practiced in the art and as described above. This antibody is labeled with the radioactive isotope ^{125}I , for example, by methods routinely practiced in the art. In a heterogeneous assay, e.g., the GST-target gene fusion protein is anchored to glutathione-agarose beads. The interactive cellular or extracellular binding partner is then added in the presence or absence of the test compound in a manner that allows interaction and binding to occur. At the end of the reaction period, unbound material can be washed away, and the labeled monoclonal antibody is added to the system and allowed to bind to the complexed components. The interaction between the target gene protein and the interactive cellular or extracellular binding partner is detected by measuring the amount of radioactivity that remains associated with the glutathione-agarose beads. A successful inhibition of the interaction by the test compound results in a decrease in measured radioactivity.

Alternatively, the GST-target gene fusion protein and the interactive cellular or extracellular binding partner are mixed together in liquid in the absence of the solid glutathione-agarose beads. The test compound is added either during or after the species are allowed to interact. This mixture is added to the glutathione-agarose beads and unbound material is washed away. Again the extent of inhibition of the target gene product/binding partner interaction is detected by adding the labeled antibody and measuring the radioactivity associated with the beads.

In another embodiment of the invention, these same techniques are employed using peptide fragments that correspond to the binding domains of the target gene product and/or the interactive cellular or extracellular binding partner (in cases where the binding partner is a protein), in place of one or both of the full length proteins. Any number of methods

5 routinely practiced in the art are used to identify and isolate the binding sites. These methods include, but are not limited to, mutagenesis of the gene encoding one of the proteins and screening for disruption of binding in a co-immunoprecipitation assay. Compensating mutations in the gene encoding the second species in the complex are then selected. Sequence analysis of the genes encoding the respective proteins reveals the mutations that correspond to the region of the protein involved in interactive binding. Alternatively, one protein is anchored to a solid surface using methods described above, and allowed to interact with and bind to its labeled binding partner, which has been treated with a proteolytic enzyme, such as trypsin. After washing, a short, labeled peptide comprising the binding domain remains associated with the solid material, and can be isolated and identified by amino acid sequencing. Also, once the gene coding for the cellular or extracellular binding partner is obtained, short gene segments are engineered to express peptide fragments of the protein, which are tested for binding activity and purified or synthesized.

10 For example, and not by way of limitation, a target gene product is anchored to a solid material as described, above, by making a GST-target gene fusion protein and allowing it to bind to glutathione agarose beads. The interactive cellular or extracellular binding partner is labeled with a radioactive isotope, such as ^{35}S , and cleaved with a proteolytic enzyme such as trypsin. Cleavage products are added to the anchored GST-target gene fusion protein and allowed to bind. After washing away unbound peptides, labeled bound material, representing the cellular or extracellular binding partner binding domain, is eluted, purified, and analyzed for amino acid sequence by well known methods. Peptides so identified are produced synthetically or fused to appropriate facilitative proteins using well known recombinant DNA technology.

5.5.1.2 Screening a Combinatorial Chemical library

25 In one embodiment of the present invention, the proteins encoded by the fungal genes identified using the methods of the present invention are isolated and expressed. These recombinant proteins are then used as targets in assays to screen libraries of compounds for potential drug candidates. The generation of chemical libraries is well known in the art. For example, combinatorial chemistry is used to generate a library of compounds to be screened in the assays described herein. A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical "building block" reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining amino acids in every possible combination to yield peptides of a given length. Millions of chemical compounds theoretically can be synthesized through such combinatorial mixings of chemical building blocks. For

example, one commentator observed that the systematic, combinatorial mixing of 100 interchangeable chemical building blocks results in the theoretical synthesis of 100 million tetrameric compounds or 10 billion pentameric compounds. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery, Background and Peptide Combinatorial Libraries," Journal of Medicinal Chemistry, Vol. 37, No. 9, 1233-1250 (1994). Other chemical libraries known to those in the art may also be used, including natural product libraries.

Once generated, combinatorial libraries are screened for compounds that possess desirable biological properties. For example, compounds which may be useful as drugs or to develop drugs would likely have the ability to bind to the target protein identified, expressed and purified as discussed above. Further, if the identified target protein is an enzyme, candidate compounds would likely interfere with the enzymatic properties of the target protein. For example, the enzymatic function of a target protein may be to serve as a protease, nuclease, phosphatase, dehydrogenase, transporter protein, transcriptional enzyme, replication component, and any other type of enzyme known or unknown. Thus, the present invention contemplates using the protein products described above to screen combinatorial chemical libraries.

In some embodiments of the present invention, the biochemical activity of the protein, as well as the chemical structure of a substrate on which the protein acts is known. In other embodiments of the present invention, the biochemical activity of the target protein is unknown and the target protein has no known substrates.

In some embodiments of the present invention, libraries of compounds are screened to identify compounds that function as inhibitors of the target gene product. First, a library of small molecules is generated using methods of combinatorial library formation well known in the art. U.S. Patent NOs. 5,463,564 and 5,574, 656, to Agrafiotis, *et al.*, entitled "System and Method of Automatically Generating Chemical Compounds with Desired Properties," the disclosures of which are incorporated herein by reference in their entireties, are two such teachings. Then the library compounds are screened to identify those compounds that possess desired structural and functional properties. U.S. Patent No. 5,684,711, the disclosure of which is incorporated herein by reference in its entirety, also discusses a method for screening libraries.

To illustrate the screening process, the target gene product, an enzyme, and chemical compounds of the library are combined and permitted to interact with one another. A labeled substrate is added to the incubation. The label on the substrate is such that a detectable signal is emitted from metabolized substrate molecules. The emission of this signal permits one to measure the effect of the combinatorial library compounds on the enzymatic activity of target enzymes by comparing it to the signal emitted in the absence of combinatorial library

compounds. The characteristics of each library compound are encoded so that compounds demonstrating activity against the enzyme can be analyzed and features common to the various compounds identified can be isolated and combined into future iterations of libraries.

Once a library of compounds is screened, subsequent libraries are generated
5 using those chemical building blocks that possess the features shown in the first round of screen to have activity against the target enzyme. Using this method, subsequent iterations of candidate compounds will possess more and more of those structural and functional features required to inhibit the function of the target enzyme, until a group of enzyme inhibitors with high specificity for the enzyme can be found. These compounds can then be further tested for their safety and
10 efficacy as antibiotics for use in mammals.

It will be readily appreciated that this particular screening methodology is exemplary only. Other methods are well known to those skilled in the art. For example, a wide variety of screening techniques are known for a large number of naturally-occurring targets when the biochemical function of the target protein is known. For example, some
15 techniques involve the generation and use of small peptides to probe and analyze target proteins both biochemically and genetically in order to identify and develop drug leads. Such techniques include the methods described in PCT publications No. WO9935494, WO9819162, WO9954728, the disclosures of which are incorporated herein by reference in their entireties.

Similar methods may be used to identify compounds which inhibit the activity
20 of proteins from organisms other than *Candida albicans* which are homologous to the *Candida albicans* target proteins described herein. For example, the proteins may be from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*, *Trichosporon beigeli*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the
25 proteins are from an organism other than *Saccharomyces cerevisiae*.
30

5.5.1.3 In vitro Enzyme Assays

GRACE methods and strains are used to develop *in vitro* assays for biochemical activities that are shown to be essential to cell viability. A number of essential genes identified
35 by the GRACE conditional expression methodologies display statistically significant similarity to biochemically characterized gene products from other organisms. For example, based on

amino acid sequence similarity, a number of essential and fungal specific genes listed in Table II are predicted to possess the following biochemical activities:

	<i>CaRHO1</i>	GTPase involved in (1,3)- β -glucan synthesis and polarity
5	<i>CaYHR118c (ORC6)</i>	Origin of replication complex subunit
	<i>CaYPL128c (TBP1)</i>	Telomere binding protein
	<i>CaYNL256w</i>	Dihydropteroate synthase
	<i>CaYKL004w (AUR1)</i>	Phosphatidylinositol: ceramide phosphoinositol transferase
	<i>CaYJL090c (DPB11)</i>	DNA polB subunit
10	<i>CaYOL149w (DCP1)</i>	mRNA decapping enzyme
	<i>CaYNL151c (RPC31)</i>	RNA polIII subunit
	<i>CaYOR148c (SPP2)</i>	RNA splicing
	<i>CaYER026c (CHO1)</i>	Phosphatidylserine synthase

15 Therefore, a number of well characterized standard *in vitro* biochemical assays (e.g., DNA binding, RNA processing, GTP binding and hydrolysis, and phosphorylation) are readily adapted for these validated drug targets. For example the validated target, *CaRHO1*, is used within a *in vitro*-based drug screen by adapting standard GTPase assays developed for a wide range of such proteins. Alternatively, novel assays are developed using biochemical
20 information pertaining to validated drug targets within our GRACE strain collection. Any assays known in the art for enzymes with similar biochemical activities (e.g., mechanism of action, class of substrate) are adapted for screening for inhibitors of the enzymes encoded by these essential *C. albicans* genes.

25 For example, a number of features make the *C. albicans* gene, *CaTBF1*, a candidate for *in vitro* assay development. *CaTBF1* shares significant homology to its *S. cerevisiae* counterpart, *TBF1*, a telomere binding factor. In addition, the DNA sequence CaTBF1p recognizes is known and is relatively short (Koering et al., Nucleic Acid Res. 28:2519-2526, which is incorporated herein by reference in its entirety), enabling inexpensive
30 synthesis of oligonucleotides corresponding to this element. Moreover since this assay only requires the target protein and a DNA fragment containing the nucleotide sequence it recognizes, only purification of CaTBF1p protein is necessary in order to develop an *in vitro* binding assay. One preferred embodiment of this *in vitro* assay involves crosslinking the DNA element to the bottom of a well, incubation of radiolabeled CaTBF1p to facilitate protein-DNA binding, a
35 series of washes to remove unbound material, and determination of the percentage of bound radiolabeled CaTBF1p. Alternatively, purified CaTBF1p is attached to the well and

radiolabeled oligonucleotides added. Drug screening, including the use of high throughput screening technique, is performed by searching for compounds that inhibit the protein-DNA binding measured in this assay.

Similarly, a second validated drug target, *CaORC6*, is used in this type of assay
5 since its *S. cerevisiae* homolog, *ORC6*, directly binds a DNA element within the origin of replication of yeast chromosomes (Mizushima et al., 2000, Genes & Development 14:1631-1641, which is incorporated herein by reference in its entirety). Biochemical purification of any of these targets could be achieved, for example, by PCR-based construction of *C. albicans* heterozygous strains in which the gene encoding the *CaORC6* protein has been modified to
10 include a carboxy-terminal hexahistidine tag enabling purification of the chimeric protein using standard Ni²⁺ affinity column chromatography techniques.

For other targets like *CaDPB11*, a homolog of which in *S. cerevisiae* encode proteins that physically associate with Sld2p (Kamimura et al., 1998, Cell Biol. 18:6102-6109, which is incorporated herein by reference in its entirety), *in vitro* assays similar to those
15 described above are developed. In addition, two-hybrid assays based on known physical interactions are developed for any validated targets within the GRACE strain collection.

The present invention also provides cell extracts useful in establishing *in vitro* assays for suitable biochemical targets. For example, in an embodiment of the present invention, GRACE-derived *C. albicans* strains are grown either under constitutive expression
20 conditions or transcription repression conditions to either overproduce or deplete a particular gene product. Cellular extracts resulting from strains incubated under these two conditions are compared with extracts prepared from identically-grown wild type strains. These extracts are then used for the rapid evaluation of targets using existing *in vitro* assays or new assays directed toward novel gene products, without having to purify the gene product. Such a whole cell
25 extract approach to *in vitro* assay development is typically necessary for targets involved in cell wall biosynthetic pathways (e. g. (1,3)- β -glucan synthesis or chitin synthesis) which involve multiple gene products that transit the secretory pathway before receiving essential post-translational modifications required for their functional activity. GRACE-derived strains for conditional expression of target genes involved in these, or other cell wall pathways (e. g. (1,6)-
30 β -glucan synthesis) enable *in vitro* assays to be performed directly in *C. albicans*.

5.5.2 Cell-based Screening Assays

Current cell-based assays used to identify or to characterize compounds for drug discovery and development frequently depend on detecting the ability of a test compound to modulate the activity of a target molecule located within a cell or located on the surface of a cell.

- 5 Most often such target molecules are proteins such as enzymes, receptors and the like. However, target molecules also include other molecules such as DNAs, lipids, carbohydrates and RNAs including messenger RNAs, ribosomal RNAs, tRNAs and the like. A number of highly sensitive cell-based assay methods are available to those of skill in the art to detect binding and interaction of test compounds with specific target molecules. However, these
- 10 methods are generally not highly effective when the test compound binds to or otherwise interacts with its target molecule with moderate or low affinity. In addition, the target molecule may not be readily accessible to a test compound in solution, such as when the target molecule is located inside the cell or within a cellular compartment such as the periplasm of a bacterial cell. Thus, current cell-based assay methods are limited in that they are not effective in identifying or
- 15 characterizing compounds that interact with their targets with moderate to low affinity or compounds that interact with targets that are not readily accessible.

The cell-based assay methods of the present invention have substantial advantages over current cell-based assays. These advantages derive from the use of sensitized cells in which the level or activity of at least one gene product required for fungal proliferation,

20 virulence, or pathogenicity (the target molecule) has been specifically reduced to the point where the presence or absence of its function becomes a rate-determining step for fungal growth, survival, proliferation, virulence, or pathogenicity. Such sensitized cells become much more sensitive to compounds that are active against the affected target molecule. For example, sensitized cells are obtained by growing a GRACE strain in the presence of a concentration of

25 inducer or repressor which provides a level of a gene product required for fungal growth, survival, proliferation, virulence, or pathogenicity such that the presence or absence of its function becomes a rate-determining step for fungal growth, survival, proliferation, virulence, or pathogenicity. Thus, cell-based assays of the present invention are capable of detecting compounds exhibiting low or moderate potency against the target molecule of interest because

30 such compounds are substantially more potent on sensitized cells than on non-sensitized cells. The effect may be such that a test compound may be two to several times more potent, at least 10 times more potent, at least 20 times more potent, at least 50 times more potent, at least 100 times more potent, at least 1000 times more potent, or even more than 1000 times more potent when tested on the sensitized cells as compared to the non-sensitized cells.

- 35 Due in part to the increased appearance of antibiotic resistance in pathogenic

microorganisms and to the significant side-effects associated with some currently used antibiotics, novel antibiotics acting at new targets are highly sought after in the art. Yet, another limitation in the current art related to cell-based assays is the problem of repeatedly identifying hits against the same kinds of target molecules in the same limited set of biological pathways.

5 This may occur when compounds acting at such new targets are discarded, ignored or fail to be detected because compounds acting at the "old" targets are encountered more frequently and are more potent than compounds acting at the new targets. As a result, the majority of antibiotics in use currently interact with a relatively small number of target molecules within an even more limited set of biological pathways.

10 The use of sensitized cells of the current invention provides a solution to the above problems in two ways. First, desired compounds acting at a target of interest, whether a new target or a previously known but poorly exploited target, can now be detected above the "noise" of compounds acting at the "old" targets due to the specific and substantial increase in potency of such desired compounds when tested on the sensitized cells of the current invention.

15 Second, the methods used to sensitize cells to compounds acting at a target of interest may also sensitize these cells to compounds acting at other target molecules within the same biological pathway. For example, expression of a gene encoding a ribosomal protein at a level such that the function of the ribosomal protein becomes rate limiting for fungal growth, survival,

20 proliferation, virulence, or pathogenicity is expected to sensitize the cell to compounds acting at that ribosomal protein to compounds acting at any of the ribosomal components (proteins or rRNA) or even to compounds acting at any target which is part of the protein synthesis pathway. Thus an important advantage of the present invention is the ability to reveal new targets and pathways that were previously not readily accessible to drug discovery methods.

25 Sensitized cells of the present invention are prepared by reducing the activity or level of a target molecule. The target molecule may be a gene product, such as an RNA or polypeptide produced from the nucleic acids required for fungal growth, survival, proliferation, virulence, or pathogenicity described herein. In addition, the target may be an RNA or polypeptide in the same biological pathway as the nucleic acids required for fungal growth,

30 survival, proliferation, virulence, or pathogenicity as described herein. Such biological pathways include, but are not limited to, enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such as the cell membrane.

Current methods employed in the arts of medicinal and combinatorial chemistries are able to make use of structure-activity relationship information derived from testing compounds in various biological assays including direct binding assays and cell-based

35 assays. Occasionally compounds are directly identified in such assays that are sufficiently

potent to be developed as drugs. More often, initial hit compounds exhibit moderate or low potency. Once a hit compound is identified with low or moderate potency, directed libraries of compounds are synthesized and tested in order to identify more potent leads. Generally these directed libraries are combinatorial chemical libraries consisting of compounds with structures
5 related to the hit compound but containing systematic variations including additions, subtractions and substitutions of various structural features. When tested for activity against the target molecule, structural features are identified that either alone or in combination with other features enhance or reduce activity. This information is used to design subsequent directed libraries containing compounds with enhanced activity against the target molecule. After one or
10 several iterations of this process, compounds with substantially increased activity against the target molecule are identified and may be further developed as drugs. This process is facilitated by use of the sensitized cells of the present invention since compounds acting at the selected targets exhibit increased potency in such cell-based assays, thus; more compounds can now be characterized providing more useful information than would be obtained otherwise.

15 Thus, it is now possible using cell-based assays of the present invention to identify or characterize compounds that previously would not have been readily identified or characterized including compounds that act at targets that previously were not readily exploited using cell-based assays. The process of evolving potent drug leads from initial hit compounds is also substantially improved by the cell-based assays of the present invention because, for the
20 same number of test compounds, more structure-function relationship information is likely to be revealed.

The method of sensitizing a cell entails selecting a suitable gene. A suitable gene is one whose expression is required for the growth, survival, proliferation, virulence, or
25 pathogenicity of the cell to be sensitized. The next step is to obtain a cell in which the level or activity of the target can be reduced to a level where it is rate limiting for growth, survival, proliferation, virulence or pathogenicity. For example, the cell may be a GRACE strain in which the selected gene is under the control of a regulatable promoter. The amount of RNA transcribed from the selected gene is limited by varying the concentration of an inducer or
30 repressor which acts on the regulatable promoter, thereby varying the activity of the promoter driving transcription of the RNA. Thus, cells are sensitized by exposing them to an inducer or repressor concentration that results in an RNA level such that the function of the selected gene product becomes rate limiting for fungal growth, survival, proliferation, virulence, or pathogenicity.

35 In one embodiment of the cell-based assays, GRACE strains, in which the sequences required for fungal growth, survival, proliferation, virulence, or pathogenicity of

Candida albicans described herein are under the control of a regulatable promoter, are grown in the presence of a concentration of inducer or repressor which causes the function of the gene products encoded by these sequences to be rate limiting for fungal growth, survival, proliferation, virulence, or pathogenicity. To achieve that goal, a growth inhibition dose curve of inducer or repressor is calculated by plotting various doses of inducer or repressor against the corresponding growth inhibition caused by the limited levels of the gene product required for fungal proliferation. From this dose-response curve, conditions providing various growth rates, from 1 to 100% as compared to inducer or repressor-free growth, can be determined. For example, if the regulatable promoter is repressed by tetracycline, the GRACE strain may be grown in the presence of varying levels of tetracycline. Similarly, inducible promoters may be used. In this case, the GRACE strains are grown in the presence of varying concentrations of inducer. For example, the highest concentration of the inducer or repressor that does not reduce the growth rate significantly can be estimated from the dose-response curve. Cellular proliferation can be monitored by growth medium turbidity via OD measurements. In another example, the concentration of inducer or repressor that reduces growth by 25% can be predicted from the dose-response curve. In still another example, a concentration of inducer or repressor that reduces growth by 50% can be calculated from the dose-response curve. Additional parameters such as colony forming units (cfu) are also used to measure cellular growth, survival and/or viability.

In another embodiment of the present invention, an individual haploid strain may similarly be used as the basis for detection of an antifungal or therapeutic agent. In this embodiment, the test organism (e.g. *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Magnaportha grisea* or any other haploid organisms represented in Table I) is a strain constructed by modifying the single allele of the target gene in one step by recombination with a promoter replacement fragment comprising a heterologous regulatable promoter, such that the expression of the gene is conditionally regulated by the heterologous promoter. Like individual diploid GRACE strains, sensitized haploid cells may similarly be used in whole cell-based assay methods to identify compounds displaying a preferential activity against the affected target.

In various embodiments, the modified strain is grown under a first set of conditions where the heterologous promoter is expressed at a relatively low level (i.e. partially repressed) and the extent of growth determined. This experiment is repeated in the presence of a test compound and a second measurement of growth obtained. The extent of growth in the presence and in the absence of the test compound are then compared to provide a first indicator value. Two further experiments are performed, using non-repressing growth conditions where the target gene is expressed at substantially higher levels than in the first set of conditions. The

extent of growth is determined in the presence and absence of the test compound under the second set of conditions to obtain a second indicator value. The first and second indicator values are then compared. If the indicator values are essentially the same, the data suggest that the test compound does not inhibit the test target. However, if the two indicator values are substantially different, the data indicates that the level of expression of the target gene product may determine the degree of inhibition by the test compound and, therefore, it is likely that the gene product is the target of that test compound. Whole-cell assays comprising collections or subsets of multiple sensitized strains may also be screened, for example, in a series of 96-well, 384-well, or even 1586-well microtiter plates, with each well containing individual strains sensitized to identify compounds displaying a preferential activity against each affected target comprising a target set or subset selected from, but not limited to the group consisting of fungal-specific, pathogen-specific, desired biochemical-function, human-homolog, cellular localization, and signal transduction cascade target sets.

Cells to be assayed are exposed to the above-determined concentrations of inducer or repressor. The presence of the inducer or repressor at this sub-lethal concentration reduces the amount of the proliferation-required gene product to the lowest amount in the cell that will support growth. Cells grown in the presence of this concentration of inducer or repressor are therefore specifically more sensitive to inhibitors of the proliferation-required protein or RNA of interest as well as to inhibitors of proteins or RNAs in the same biological pathway as the proliferation-required protein or RNA of interest but not specifically more sensitive to inhibitors of unrelated proteins or RNAs.

Cells pretreated with sub-inhibitory concentrations of inducer or repressor, which therefore contain a reduced amount of proliferation-required target gene product, are used to screen for compounds that reduce cell growth. The sub-lethal concentration of inducer or repressor may be any concentration consistent with the intended use of the assay to identify candidate compounds to which the cells are more sensitive than are control cells in which this gene product is not rate-limiting. For example, the sub-lethal concentration of the inducer or repressor may be such that growth inhibition is at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60% at least about 75%, , at least 80%, at least 90%, at least 95% or more than 95%. Cells which are pre-sensitized using the preceding method are more sensitive to inhibitors of the target protein because these cells contain less target protein to inhibit than wild-type cells.

It will be appreciated that similar methods may be used to identify compounds which inhibit virulence or pathogenicity. In such methods, the virulence or

pathogenicity of cells exposed to the candidate compound which express rate limiting levels of a gene product involved in virulence or pathogenicity is compared to the virulence or pathogenicity of cells exposed to the candidate compound in which the levels of the gene product are not rate limiting. Virulence or pathogenicity may be measured using the techniques described herein.

In another embodiment of the cell-based assays of the present invention, the level or activity of a gene product required for fungal growth, survival, proliferation, virulence, or pathogenicity is reduced using a mutation, such as a temperature sensitive mutation, in the sequence required for fungal growth, survival, proliferation, virulence, or pathogenicity and an inducer or repressor level which, in conjunction with the temperature sensitive mutation, provides levels of the gene product required for fungal growth, survival, proliferation, virulence, or pathogenicity which are rate limiting for proliferation. Growing the cells at an intermediate temperature between the permissive and restrictive temperatures of the temperature sensitive mutant where the mutation is in a gene required for fungal growth, survival, proliferation, virulence, or pathogenicity produces cells with reduced activity of the gene product required for growth, survival, proliferation, virulence, or pathogenicity. The concentration of inducer or repressor is chosen so as to further reduces the activity of the gene product required for fungal growth, survival, proliferation, virulence, or pathogenicity. Drugs that may not have been found using either the temperature sensitive mutation or the inducer or repressor alone may be identified by determining whether cells in which expression of the nucleic acid encoding the proliferation-required gene product has been reduced and which are grown at a temperature between the permissive temperature and the restrictive temperature are substantially more sensitive to a test compound than cells in which expression of the gene product required for fungal growth, survival, proliferation, virulence, or pathogenicity has not been reduced and which are grown at a permissive temperature. Also drugs found previously from either the use of the inducer or repressor alone or the temperature sensitive mutation alone may have a different sensitivity profile when used in cells combining the two approaches, and that sensitivity profile may indicate a more specific action of the drug in inhibiting one or more activities of the gene product.

Temperature sensitive mutations may be located at different sites within a gene and may lie within different domains of the protein. For example, the *dnaB* gene of *Escherichia coli* encodes the replication fork DNA helicase. DnaB has several domains, including domains for oligomerization, ATP hydrolysis, DNA binding, interaction with primase, interaction with DnaC, and interaction with DnaA. Temperature sensitive mutations in different domains of DnaB confer different phenotypes at the restrictive

temperature, which include either an abrupt stop or a slow stop in DNA replication either with or without DNA breakdown (Wechsler, J.A. and Gross, J.D. 1971 *Escherichia coli* mutants temperature-sensitive for DNA synthesis. Mol. Gen. Genetics 113:273-284) and termination of growth or cell death. Thus, temperature sensitive mutations in different
5 domains of the protein may be used in conjunction with GRACE strains in which expression of the protein is under the control of a regulatable promoter.

It will be appreciated that the above method may be performed with any mutation which reduces but does not eliminate the activity or level of the gene product which is required for fungal growth, survival, proliferation, virulence, or pathogenicity.

10 When screening for antimicrobial agents against a gene product required for fungal growth, survival, proliferation, virulence, or pathogenicity, growth inhibition, virulence or pathogenicity of cells containing a limiting amount of that gene product can be assayed. Growth inhibition can be measured by directly comparing the amount of growth, measured by the optical density of the culture relative to uninoculated growth medium,
15 between an experimental sample and a control sample. Alternative methods for assaying cell proliferation include measuring green fluorescent protein (GFP) reporter construct emissions, various enzymatic activity assays, and other methods well known in the art. Virulence and pathogenicity may be measured using the techniques described herein.

It will be appreciated that the above method may be performed in solid
20 phase, liquid phase, a combination of the two preceding media, or *in vivo*. For example, cells grown on nutrient agar containing the inducer or repressor which acts on the regulatable promoter used to express the proliferation required gene product may be exposed to compounds spotted onto the agar surface. A compound's effect may be judged from the diameter of the resulting killing zone, the area around the compound application
25 point in which cells do not grow. Multiple compounds may be transferred to agar plates and simultaneously tested using automated and semi-automated equipment including but not restricted to multi-channel pipettes (for example the Beckman Multimek) and multi-channel spotters (for example the Genomic Solutions Flexys). In this way multiple plates and thousands to millions of compounds may be tested per day.

30 The compounds are also tested entirely in liquid phase using microtiter plates as described below. Liquid phase screening may be performed in microtiter plates containing 96, 384, 1536 or more wells per microtiter plate to screen multiple plates and thousands to millions of compounds per day. Automated and semi-automated equipment are used for addition of reagents (for example cells and compounds) and for determination
35 of cell density.

The compounds are also tested *in vivo* using the methods described herein.

It will be appreciated that each of the above cell-based assays may be used to identify compounds which inhibit the activity of gene products from organisms other than *Candida albicans* which are homologous to the *Candida albicans* gene products described
5 herein. For example, the target gene products may be from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*, *Trichosporon beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia*
10 *corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the gene products are from an organism other than *Saccharomyces cerevisiae*.

15 5.5.2.1 Cell-Based Assays Using GRACE Strains

GRACE strains in which one allele of a gene required for fungal growth, survival, proliferation, virulence, or pathogenicity is inactivated while the other allele is under the control of a regulatable promoter are constructed using the methods described
20 herein. For the purposes of the present example, the regulatable promoter may be the tetracycline regulated promoter described herein, but it will be appreciated that any regulatable promoter may be used.

In one embodiment of the present invention, an individual GRACE strain is used as the basis for detection of a therapeutic agent active against a diploid pathogenic fungal cell. In this embodiment, the test organism is a GRACE strain having a modified
25 allelic gene pair, where the first allele of the gene has been inactivated by the insertion of, or replacement by, a nucleotide sequence encoding an expressible, dominant selectable marker and the second allele has been modified, by recombination, to place the second allele under the controlled expression of a heterologous promoter. This test GRACE strain is then
30 grown under a first set of conditions where the heterologous promoter is expressed at a relatively low level ("repressing") and the extent of growth determined. This measurement may be carried out using any appropriate standard known to those skilled in the art including optical density, wet weight of pelleted cells, total cell count, viable count, DNA content, and the like. This experiment is repeated in the presence of a test compound and a
35 second measurement of growth obtained. The extent of growth in the presence and in the absence of the test compound, which can conveniently be expressed in terms of indicator

values, are then compared. A dissimilarity in the extent of growth or indicator values provides an indication that the test compound may interact with the target essential gene product.

To gain more information, two further experiments are performed, using a second set of "non-repressing" growth conditions where the second allele, under the control of the heterologous promoter, is expressed at a level substantially higher than in the first set of conditions described above. The extent of growth or indicator values is determined in the presence and absence of the test compound under this second set of conditions. The extent of growth or indicator values in the presence and in the absence of the test compound are then compared. A dissimilarity in the extent of growth or indicator values provides an indication that may interact with the target essential gene product.

Furthermore, the extent of growth in the first and in the second set of growth conditions can also be compared. If the extent of growth is essentially the same, the data suggest that the test compound does not inhibit the gene product encoded by the modified allelic gene pair carried by the GRACE strain tested. However, if the extent of growth are substantially different, the data indicate that the level of expression of the subject gene product may determine the degree of inhibition by the test compound and, therefore, it is likely that the subject gene product is the target of that test compound.

Although each GRACE strain can be tested individually, it will be more efficient to screen entire sets or subsets of a GRACE strain collection at one time. Therefore in one aspect of this invention, arrays may be established, for example in a series of 96-well microtiter plates, with each well containing a single GRACE strain. In one representative, but not limiting approach, four microtiter plates are used, comprising two pairs where the growth medium in one pair supports greater expression of the heterologous promoter controlling the remaining active allele in each strain, than the medium in the other pair of plates. One member of each pair is supplemented with a compound to be tested and measurements of growth of each GRACE strain is determined using standard procedures to provide indicator values for each isolate tested. The collection of diploid pathogenic GRACE strains used in such a method for screening for therapeutic agents may comprise, for example, a substantially complete set of all the modified allelic gene pairs of the organism, the substantially complete set of all the modified allelic essential gene pairs of the organism or the collection may be selected from a subset of GRACE strains selected from, but not limited to the group consisting of fungal-specific, pathogen-specific, desired biochemical-function, human-homolog, cellular localization, and signal transduction cascade target sets.

The GRACE strains are grown in medium comprising a range of tetracycline concentrations to obtain the growth inhibitory dose-response curve for each strain. First, seed cultures of the GRACE strains are grown in the appropriate medium. Subsequently, aliquots of the seed cultures are diluted into medium containing varying concentrations of tetracycline. For example, the GRACE strains may be grown in duplicate cultures containing two-fold serial dilutions of tetracycline. Additionally, control cells are grown in duplicate without tetracycline. The control cultures are started from equal amounts of cells derived from the same initial seed culture of a GRACE strain of interest. The cells are grown for an appropriate period of time and the extent of growth is determined using any appropriate technique. For example, the extent of growth may be determined by measuring the optical density of the cultures. When the control culture reaches mid-log phase the percent growth (relative to the control culture) for each of the tetracycline containing cultures is plotted against the log concentrations of tetracycline to produce a growth inhibitory dose response curve for tetracycline. The concentration of tetracycline that inhibits cell growth to 50% (IC_{50}) as compared to the 0 mM tetracycline control (0% growth inhibition) is then calculated from the curve. Alternative methods of measuring growth are also contemplated. Examples of these methods include measurements of proteins, the expression of which is engineered into the cells being tested and can readily be measured. Examples of such proteins include green fluorescent protein (GFP) and various enzymes.

Cells are pretreated with the selected concentration of tetracycline and then used to test the sensitivity of cell populations to candidate compounds. For example, the cells may be pretreated with a concentration of tetracycline which inhibits growth by at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 75%, at least 80%, at least 90%, at least 95% or more than 95%. The cells are then contacted with the candidate compound and growth of the cells in tetracycline containing medium is compared to growth of the control cells in medium which lacks tetracycline to determine whether the candidate compound inhibits growth of the sensitized cells (i.e. the cells grown in the presence of tetracycline). For example, the growth of the cells in tetracycline containing medium may be compared to the growth of the cells in medium lacking tetracycline to determine whether the candidate compound inhibits the growth of the sensitized cells (i.e. the cells grown in the presence of tetracycline) to a greater extent than the candidate compound inhibits the growth of cells grown in the absence of tetracycline. For example, if a significant difference in growth is observed between the sensitized cells (i.e. the cells grown in the presence of tetracycline) and the non-sensitized cells (i.e. the cells grown in the absence of tetracycline),

the candidate compound may be used to inhibit the proliferation of the organism or may be further optimized to identify compounds which have an even greater ability to inhibit the growth, survival, or proliferation of the organism.

Similarly, the virulence or pathogenicity of cells exposed to a candidate
5 compound which express a rate limiting amount of a gene product required for virulence or pathogenicity may be compared to the virulence or pathogenicity of cells exposed to the candidate compound in which the level of expression of the gene product required for virulence or pathogenicity is not rate limiting. In such methods, test animals are challenged with the GRACE strain and fed a diet containing the desired amount of tetracycline and the
10 candidate compound. Thus, the GRACE strain infecting the test animals expresses a rate limiting amount of a gene product required for virulence or pathogenicity (i.e. the GRACE cells in the test animals are sensitized). Control animals are challenged with the GRACE strain and are fed a diet containing the candidate compound but lacking tetracycline. The virulence or pathogenicity of the GRACE strain in the test animals is compared to that in
15 the control animals. For example, the virulence or pathogenicity of the GRACE strain in the test animals may be compared to that in the control animals to determine whether the candidate compound inhibits the virulence or pathogenicity of the sensitized GRACE cells (i.e. the cells in the animals whose diet included tetracycline) to a greater extent than the candidate compound inhibits the growth of the GRACE cells in animals whose diet lacked
20 tetracycline. For example, if a significant difference in growth is observed between the sensitized GRACE cells (i.e. the cells in animals whose diet included tetracycline) and the non-sensitized cells (i.e. the GRACE cells animals whose diet did not include tetracycline), the candidate compound may be used to inhibit the virulence or pathogenicity of the organism or may be further optimized to identify compounds which have an even greater
25 ability to inhibit the virulence or pathogenicity of the organism. Virulence or pathogenicity may be measured using the techniques described therein.

It will be appreciated that the above cell-based assays may be used to identify compounds which inhibit the activity of gene products from organisms other than
30 *Candida albicans* which are homologous to the *Candida albicans* gene products described herein. For example, the gene products may be from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*,
35 *Trichosporon beigeli*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*,

Magnaporthe grisea, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the gene products are from an organism other than *Saccharomyces cerevisiae*.

The cell-based assay described above may also be used to identify the
5 biological pathway in which a nucleic acid required for fungal proliferation, virulence or pathogenicity or the gene product of such a nucleic acid lies. In such methods, cells expressing a rate limiting level of a target nucleic acid required for fungal proliferation, virulence or pathogenicity and control cells in which expression of the target nucleic acid is not rate limiting are contacted with a panel of antibiotics known to act in various pathways.
10 If the antibiotic acts in the pathway in which the target nucleic acid or its gene product lies, cells in which expression of target nucleic acid is rate limiting will be more sensitive to the antibiotic than cells in which expression of the target nucleic acid is not rate limiting.

As a control, the results of the assay may be confirmed by contacting a panel
of cells in which the levels of many different genes required for proliferation, virulence or
15 pathogenicity, including the target gene, is rate limiting. If the antibiotic is acting specifically, heightened sensitivity to the antibiotic will be observed only in the cells in which the target gene is rate limiting (or cells in which genes in the same pathway as the target gene is rate limiting) but will not be observed generally in which a gene product required for proliferation, virulence or pathogenicity is rate limiting.

20 It will be appreciated that the above method for identifying the biological pathway in which a nucleic acid required for proliferation, virulence or pathogenicity lies may be applied to nucleic acids from organisms other than *Candida albicans* which are homologous to the *Candida albicans* nucleic acids described herein. For example, the nucleic acids may be from animal fungal pathogens such as *Aspergillus fumigatus*,
25 *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatiditis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Phneumocystis carinii*, *Trichosporon beigeli*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant
30 fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the nucleic acids are from an organism other than *Saccharomyces cerevisiae*.

Similarly, the above method may be used to determine the pathway on which
35 a test compound, such as a test antibiotic acts. A panel of cells, each of which expresses a rate limiting amount of a gene product required for fungal proliferation, virulence or

pathogenicity where the gene product lies in a known pathway, is contacted with a compound for which it is desired to determine the pathway on which it acts. The sensitivity of the panel of cells to the test compound is determined in cells in which expression of the nucleic acid encoding the gene product required for proliferation, virulence or pathogenicity is at a rate limiting level and in control cells in which expression of the gene product required for proliferation, virulence or pathogenicity is not at a rate limiting level. If the test compound acts on the pathway in which a particular gene product required for proliferation, virulence, or pathogenicity lies, cells in which expression of that particular gene product is at a rate limiting level will be more sensitive to the compound than the cells in which gene products in other pathways are at a rate limiting level. In addition, control cells in which expression of the particular gene required for fungal proliferation, virulence or pathogenicity is not rate limiting will not exhibit heightened sensitivity to the compound. In this way, the pathway on which the test compound acts may be determined.

It will be appreciated that the above method for determining the pathway on which a test compound acts may be applied to organisms other than *Candida albicans* by using panels of cells in which the activity or level of gene products which are homologous to the *Candida albicans* gene products described herein is rate limiting. For example, the gene products may be from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Pneumocystis carinii*, *Trichosporon beigeli*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the gene products are from an organism other than *Saccharomyces cerevisiae*. Example 6.4, *infra*, provided below describes one method for performing such assays.

One skilled in the art will appreciate that further optimization of the assay conditions, such as the concentration of inducer or repressor used to produce rate limiting levels of a gene product required for fungal proliferation, virulence or pathogenicity and/or the growth conditions used for the assay (for example incubation temperature and medium components) may further increase the selectivity and/or magnitude of the antibiotic sensitization exhibited.

It will be appreciated that the above methods for identifying the pathway in which a gene required for growth, survival, proliferation, virulence or pathogenicity lies or

the pathway on which an antibiotic acts may be performed using organisms other than *Candida albicans* in which gene products homologous to the *Candida albicans* gene products described herein are rate limiting. For example, the gene products may be from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*,
5 *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Pneumocystis carinii*, *Trichosporon beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria*
10 *triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the gene products are from an organism other than *Saccharomyces cerevisiae*.

Furthermore, as discussed above, panels of GRACE strains may be used to characterize the point of intervention of any compound affecting an essential biological
15 pathway including antibiotics with no known mechanism of action.

Another embodiment of the present invention is a method for determining the pathway against which a test antibiotic compound is active, in which the activity of proteins or nucleic acids involved in pathways required for fungal growth, survival, proliferation, virulence or pathogenicity is reduced by contacting cells with a sub-lethal
20 concentration of a known antibiotic which acts against the protein or nucleic acid. The method is similar to those described above for determining which pathway a test antibiotic acts against, except that rather than reducing the activity or level of a gene product required for fungal proliferation, virulence or pathogenicity by expressing the gene product at a rate limiting amount in a GRACE strain, the activity or level of the gene product is reduced
25 using a sub-lethal level of a known antibiotic which acts against the gene product.

Growth inhibition resulting from the presence of sub-lethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%,
30 or at least about 75%, at least 80%, at least 90%, at least 95% or more than 95%.

Alternatively, the sub-lethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

Cells are contacted with a combination of each member of a panel of known antibiotics at a sub-lethal level and varying concentrations of the test antibiotic. As a
35 control, the cells are contacted with varying concentrations of the test antibiotic alone. The

IC₅₀ of the test antibiotic in the presence and absence of the known antibiotic is determined. If the IC₅₀s in the presence and absence of the known drug are substantially similar, then the test drug and the known drug act on different pathways. If the IC₅₀s are substantially different, then the test drug and the known drug act on the same pathway.

5 Similar methods may be performed using known antibiotics which act on a gene product homologous to the *Candida albicans* sequences described herein. The homologous gene product may be from animal fungal pathogens such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*,
10 *Fusarium oxysporum*, *Histoplasma capsulatum*, *Pneumocystis carinii*, *Trichosporon beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the
15 gene products are from an organism other than *Saccharomyces cerevisiae*.

 Another embodiment of the present invention is a method for identifying a candidate compound for use as an antibiotic in which the activity of target proteins or nucleic acids involved in pathways required for fungal proliferation, virulence or pathogenicity is reduced by contacting cells with a sub-lethal concentration of a known
20 antibiotic which acts against the target protein or nucleic acid. The method is similar to those described above for identifying candidate compounds for use as antibiotics except that rather than reducing the activity or level of a gene product required for proliferation, virulence or pathogenicity using GRACE strains which express a rate limiting level of the gene product, the activity or level of the gene product is reduced using a sub-lethal level of
25 a known antibiotic which acts against the proliferation required gene product.

 The growth inhibition from the sub-lethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at
30 least about 75%, or more.

 Alternatively, the sub-lethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

 In order to characterize test compounds of interest, cells are contacted with a
35 panel of known antibiotics at a sub-lethal level and one or more concentrations of the test compound. As a control, the cells are contacted with the same concentrations of the test

compound alone. The IC_{50} of the test compound in the presence and absence of the known antibiotic is determined. If the IC_{50} of the test compound is substantially different in the presence and absence of the known drug then the test compound is a good candidate for use as an antibiotic. As discussed above, once a candidate compound is identified using the
5 above methods its structure may be optimized using standard techniques such as combinatorial chemistry.

Similar methods may be performed using known antibiotics which act on a gene product homologous to the *Candida albicans* sequences described herein. The homologous gene product may be from animal fungal pathogens such as *Aspergillus*
10 *fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Pneumocystis carinii*, *Trichosporon beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, or *Absidia corymbigera*, or the plant fungal pathogens, such as *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe*
15 *grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, *Ustilago maydis*, or any species falling within the genera of any of the above species. In some embodiments, the gene products are from an organism other than *Saccharomyces cerevisiae*.

An exemplary target gene product is encoded by *CaTBF1*. A number of features make this *C. albicans* gene product a valuable drug target. First, the protein
20 encoded by *CaTBF1* is compatible with *in vitro* high throughput screening of compounds that inhibit its activity. Modulated expression of this gene product in whole cell assays could be performed in parallel with *in vitro* assays to broaden the spectrum of possible inhibitory compounds identified. In addition, demonstration of the predicted physical interaction between *CaTbf1p* and chromosomal telomerases could be used to develop two-
25 hybrid assays for drug screening purposes. Finally, because *CaTBF1* is a fungal specific gene, its nucleotide sequence could serve in designing PCR-based diagnostic tools for fungal infection.

Other validated drug targets included in the GRACE-derived strain collection that represent preferred drug targets include the products encoded by the following
30 *C. albicans* genes: *CaRHO1*, *CaERG8*, *CaAUR1*, and *CaCHO1*, as well as those encoded by SEQ ID NOs.:1-62. The ability to manipulate these genes using GRACE methods of the present invention will improve drug screening practices now in use that are designed to identify inhibitors of these critical gene products.

In another embodiment of the present invention, all potential drug targets of
35 a pathogen could be screened simultaneously against a library of compounds using, for

example a 96 well microtiter plate format, where growth, measured by optical density or pellet size after centrifugation, may be determined for each well. A genomic approach to drug screening eliminates reliance upon potentially arbitrary and artificial criteria used in evaluating which target to screen and instead allows all potential targets to be screened.

- 5 This approach not only offers the possibility of identifying specific compounds which inhibit a preferred process (*e. g.* cell wall biosynthetic gene products) but also the possibility of identifying all fungicidal compounds within that library and linking them to their cognate cellular targets.

- In still another embodiment of the present invention, GRACE strains could
- 10 be screened to identify synthetic lethal mutations, and thereby uncover a potentially novel class of drug targets of significant therapeutic value. For example two separate genes may encode homologous proteins that participate in a common and essential cellular function, where the essential nature of this function will only become apparent upon inactivation of both family members. Accordingly, examination of the null phenotype of each gene
- 15 separately would not reveal the essential nature of the combined gene products, and consequently, this potential drug target would not be identified. Provided the gene products are highly homologous to one another, compounds found to inhibit one family member are likely to inhibit the other and are therefore predicted to approximate the synthetic growth inhibition demonstrated genetically. In other cases however, synthetic lethality may uncover
- 20 seemingly unrelated (and often nonessential) processes, which when combined produce a synergistic growth impairment (cell death). For example, although disruption of the *S. cerevisiae* gene *RVS161* does not present any discernable vegetative growth phenotype in yeast carrying this single mutation, at least 9 other genes are known to display a synthetic lethal effect when combined with inactivation of *RVS161*. These genes participate in
- 25 processes ranging from cytoskeletal assembly and endocytosis, to signal transduction and lipid metabolism and identifies multiple avenues to pursuing a combination drug target strategy. A directed approach to uncovering synthetic lethal interactions with essential and nonessential drug targets is now performed where a GRACE strain or heterozygote strain is identified as displaying an enhanced sensitivity to the tested compound, not because it
- 30 expresses a reduced level of activity for the drug target, but because its mutation is synthetically lethal in combination with inhibition of a second drug target. Discerning whether the compound specifically inhibits the drug target in the sensitized GRACE strain or heterozygote strain or a second target may be achieved by screening the entire GRACE or heterozygote strain sets for additional mutant strains displaying equal or greater sensitivity
- 35 to the compound, followed by genetic characterization of a double mutant strain

demonstrating synthetic lethality between the two mutations.

5.5.2.2 Screening for Non-antifungal Therapeutic Agents With GRACE Strains

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The biochemical similarity existing between pathogenic fungi and the mammalian hosts they infect limits the range of clinically useful antimycotic compounds. However, this similarity can be exploited using a GRACE strain collection to facilitate the discovery of therapeutics that are not used as antimycotics, but are useful for treatment a wide-range of diseases, such as cancer, inflammation, etc.

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In this embodiment of the invention, fungal genes that are homologous to disease-causing genes in an animal or plant, are selected and GRACE strains of this set of genes are used for identification of compounds that display potent and specific bioactivity towards the products of these genes, and therefore have potential medicinal value for the treatment of diseases. Essential and non-essential genes and the corresponding GRACE strains carrying modified allelic pairs of such genes are useful in this embodiment of the invention. It has been predicted that as many as 40% of the genes found within the *C. albicans* genome share human functional homologs. It has also been predicted that as many as 1% of human genes are involved in human diseases and therefore may serve as potential drug targets. Accordingly, many genes within the GRACE strain collection are homologs to disease-causing human genes and compounds that specifically inactivate individual members of this gene set may in fact have alternative therapeutic value. The invention provides a pluralities of GRACE strains in which the modified alleles are fungal genes that share sequence, structural and/or functional similarities to genes that are associated with one or more diseases of the animal or plant.

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For example, much of the signal transduction machinery that promotes cell cycle progression and is often perturbed in a variety of cancers is conserved in fungi. Many of these genes encode for cyclins, cyclin-dependent kinases (CDK), CDK inhibitors, phosphatases, and transcription factors that are both structurally and functionally related. As a result, compounds found to display specificity towards any of these functional classes of proteins could be evaluated by secondary screens to test for potential anticancer activity. However, cytotoxic compounds identified in this way need not act on cancer causing targets to display therapeutic potential. For example the taxol family of anti-cancer compounds, which hold promise as therapeutics for breast and ovarian cancers, bind tubulin and promote microtubule assembly, thereby disrupting normal microtubule dynamics. Yeast

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tubulin displays similar sensitivity to taxol, suggesting that additional compounds affecting other fundamental cellular processes shared between yeast and man could similarly be identified and assessed for antitumor activity.

The phenomenon of pathogenesis extends far beyond the taxonomic borders of microbes and ultimately reflects the underlying physiology. In many ways, the phenomenon of cancer is analogous to the process of pathogenesis by an opportunistic pathogen such as *C. albicans*. Both are non-infectious diseases caused by either the body's own cells, or microbes from its natural fauna. These cells grow in a manner unchecked by the immune system and in both cases disease manifests itself by colonization of vital organs and eventual tissue damage resulting in death. Effective drug-based treatment is also elusive for both diseases primarily because the causative agent in both cases is highly related to the host.

In fact, a number of successful therapeutic drugs affecting processes unrelated to cancer have also been discovered through anti-fungal drug screening programs. One clinically-important class of compounds includes the immunosuppressant molecules rapamycin, cyclosporin A, and FK506, which inhibit conserved signal transduction components. Cyclosporin A and FK506, form distinct drug-prolyl isomerase complexes (CyPA- Cyclosporin A and FKBP12-FK506 respectively) which bind and inactivate the regulatory subunit of the calcium and calmodulin-dependent phosphatase, calcineurin. Rapamycin also complexes with FKBP12, but this drug-protein complex also binds to the TOR family of phosphatidylinositol kinases to inhibit translation and cell cycle progression. In each case, both the mechanism of drug action, and the drug targets themselves are highly conserved from yeast to humans.

The identification of *C. albicans* drug targets, and grouping the targets into essential-gene, fungal-specific, and pathogen-specific target sets provide the basis for the development of whole-cell screens for compounds that interact with and inhibit individual members of any of these targets. Therefore, similar analyses can be used to identify other sets of GRACE strains having modified allelic pairs of genes encoding drug targets with other specific common functions or attributes. For example, GRACE strain subsets can be established which comprise gene targets that are highly homologous to human genes, or gene targets that display a common biochemical function, enzymatic activity, or that are involved in carbon compound catabolism, biosynthesis, transport of molecules (transporter activity), cellular localization, signal transduction cascades, cell cycle control, cell adhesion, transcription, translation, DNA replication, etc.

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5.5.2.3 Target Gene Dosage-Based Whole Cell Assays

Experiments involving modulating the expression levels of the encoding gene to reveal phenotypes from which gene function may be inferred can be carried out in a pathogenic diploid fungus, such as *Candida albicans*, using the strains and methods of the present intention. The principle of drug-target-level variation in drug screening involves modulating the expression level of a drug target to identify specific drug resistance or drug sensitivity phenotypes, thereby linking a drug target to a particular compound. Often, these phenotypes are indicative of the target gene encoding the bona fide drug target of this compound. In examples where this is not the case, the candidate target gene may nonetheless provide important insight into the true target gene that is functioning either in a pathway or process related to that inhibited by the compound (*e.g.* producing synthetic phenotype), or instead functioning as a drug resistance mechanism associated with the identified compound.

Variation of the expression levels of the target protein is also incorporated within both drug screening and drug target identification procedures. The total, cellular expression level of a gene product in a diploid organism is modified by disrupting one allele of the gene encoding that product, thereby reducing its functional activity in half, creating a "haploinsufficient" phenotype. A heterozygous *S. cerevisiae* strain collection has been used in such a haploinsufficiency screen to link drug-based resistance and hypersensitive phenotypes to heterozygous drug targets. Nonessential genes are screened directly using a haploid deletion strain collection against a compound library for specific phenotypes or "chemotypes." However, this procedure cannot be used in a haploid organism where the target gene is an essential one.

The expression level of a given gene product is also elevated by cloning the gene into a plasmid vector that is maintained at multiple copies in the cell. Overexpression of the encoding gene is also achieved by fusing the corresponding open reading frame of the gene product to a more powerful promoter carried on a multicopy plasmid. Using these strategies, a number of overexpression screens have been successfully employed in *S. cerevisiae* to discover novel compounds that interact with characterized drug targets as well as to identify the protein targets bound by existing therapeutic compounds.

The GRACE strain collection replaces the surrogate use of *S. cerevisiae* in whole cell drug screening by providing a dramatic range in gene expression levels for drug targets directly within the pathogen (Fig. 5). In one embodiment of the invention, this is achieved using the *C. albicans*-adapted tetracycline promoter system to construct GRACE strains. Northern Blot analysis of 30 different GRACE strains grown under nonrepressing

conditions (i.e. no tetracycline) reveals that 83% of conditionally expressed genes tested maintain an overexpression level greater than or equal to 3 fold of wild type, and 60% of all genes examined express greater than or equal to 5 times that of the wild type *C. albicans* strain used for GRACE strain construction. As each GRACE strain is in fact heterozygous, this expression range is presumably doubled if compared against their respective heterozygote strain. For most GRACE strains then, this represents an elevated expression level rivaling that typically achieved in *S. cerevisiae* using standard 2μ -based multicopy plasmids, and an absolute level of constitutive expression comparable to that provided by the *CaACT1* promoter. Therefore, the GRACE strain collections of the invention are not only useful in target validation under repressing conditions, but are also useful as a collection of strains overexpressing these same validated drug targets under nonrepressing conditions for whole cell assay development and drug screening.

Variation in the level of expression of a target gene product in a GRACE strain is also used to explore resistance to antimycotic compounds. Resistance to existing antifungal therapeutic agents reflects both the limited number of antifungal drugs available and the alarming dependence and reliance clinicians have in prescribing them. For example, dependence on azole-based compounds such as fluconazole for the treatment of fungal infections, has dramatically undermined the clinical therapeutic value for this compound. The GRACE strain collection is used to combat fluconazole resistance by identifying gene products that interact with the cellular target of fluconazole. Such products are used to identify drug targets which, when inactivated in concert with fluconazole, provide a synergistic effect and thereby overcome resistance to fluconazole seen when this compound is used alone. This is accomplished, for example, by using the GRACE strain collection to overexpress genes that enhance drug resistance. Such genes include novel or known plasma membrane exporters including ATP-binding cassette (ABC) transporters and multidrug resistance (MDR) efflux pumps, pleiotropic drug resistance (PDR) transcription factors, and protein kinases and phosphatases. Alternatively, genes specifically displaying a differential drug sensitivity are identified by screening GRACE strains expressing reduced levels (either by haploinsufficiency or threshold expression via the tetracycline promoter) individual members of the target set. Identifying such genes provides important clues to drug resistance mechanisms that could be targeted for drug-based inactivation to enhance the efficacy of existing antifungal therapeutics.

In another aspect of the present invention, overexpression of the target gene for whole cell assay purposes is supported with promoters other than the tetracycline promoter system. (see Section 5.3.1) For example, the *CaPGK1* promoter is used to

overexpress *C. albicans* drug targets genes. In *S. cerevisiae*, the PGK1 promoter is known to provide strong constitutive expression in the presence of glucose. See, Guthrie, C., and G. R. Fink. 1991. Guide to yeast genetics and molecular biology. Methods Enzymol. 194:373-398. A preliminary analysis of five *C. albicans* genes placed under the control of the

5 *CaPGK1* promoter (*CaKRE9*, *CaERG11*, *CaALG7*, *CaTUB1* and *CaAUR1*) revealed dramatic overexpression versus wild type as judged by Northern blot analysis. The level of overexpression achieved for all genes exceeds that obtained by the tetracycline promoter by 3-4 fold. Moreover, *CaAUR1*, which was not overexpressed significantly when

10 constitutively expressed using the tetracycline promoter, was overexpressed 5-fold relative to wild type *CaAUR1* expression levels, suggesting that the *CaPGK1* promoter is useful in overexpressing genes normally not overexpressed by the tetracycline promoter.

In another aspect of the present invention, intermediate expression levels of individual drug targets within the GRACE strain collection may be engineered to provide strains tailored for the development of unique whole cell assays. In this embodiment of the

15 invention, GRACE strains are grown in a medium containing a tetracycline concentration determined to provide only a partial repression of transcription. Under these conditions, it is possible to maintain an expression level between that of the constitutively expressed overproducing strain and that of wild type strain, as well as levels of expression lower than that of the wild-type strain. That is, it is possible to titrate the level of expression to the

20 minimum required for cell viability. By repressing gene expression to this critical state, novel phenotypes, resembling those produced by a partial loss of function mutation (*i.e.* phenocopies of hypomorphic mutants) may be produced and offer additional target expression levels applicable for whole cell assay development and drug screening. Repressing expression of the remaining allele of an essential gene to the threshold level

25 required for viability, therefore will provide a strain with enhanced sensitivity toward compounds active against this essential gene product.

In order to demonstrate the utility of target level expression in whole cell assays for drug screening, both a *CaHIS3* heterozygote strain and a tetracycline promoter-regulated *CaHIS3* GRACE strain were compared against a wild type (diploid) *CaHIS3*

30 strain for sensitivity towards the 3-aminotriazole (3-AT) (Example 6.3). The data derived from these experiments clearly indicate that distinct levels of target gene products synthesized within the pathogen could be directly applied in whole cell assay based drug screens to identify novel antifungal compounds active against novel drug targets validated using the GRACE method.

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5.5.2.4 Uses of Tagged strains

In still another aspect of the present invention, unique oligonucleotide sequence tags or "bar codes" are incorporated into individual mutant strains included within a heterozygous strain collection of validated targets. The presence of these sequence tags enables an alternative whole cell assay approach to drug screening. Multiple target strains may be screened simultaneously in a mixed population (rather than separately) to identify phenotypes between a particular drug target and its inhibitory agent.

Large-scale parallel analyses are performed using mixed populations of the entire bar coded heterozygous essential strain collection target set and comparing the relative representation of individual strains within a mixed population prior to and after growth in the presence of a compound. Drug-dependent depletion or overrepresentation of a unique bar-coded strain is determined by PCR-amplifying and fluorescently labeling all bar codes within the mixed population and hybridizing the resulting PCR products to an array of complementary oligonucleotides. Differential representation between bar coded strains indicates gene-specific hypersensitivity or resistance and suggests the corresponding gene product may represent the molecular target of the compound tested.

In one specific embodiment, the mutant strains are GRACE strains, and each of the GRACE strains of the set comprises a unique molecular tag, which, generally, is incorporated within the cassette used to replace the first allele of the gene pair to be modified. Each molecular tag is flanked by primer sequences which are common to all members of the set being tested. Growth is carried out in repressive and non-repressive media, in the presence and absence of the compound to be tested. The relative growth of each strain is assessed by carrying out simultaneous PCR amplification of the entire collection of embedded sequence tags.

In one non-limiting aspect of the present invention, the PCR amplification is performed in an asymmetric manner with fluorescent primers and the resulting single stranded nucleic acid product hybridized to an oligonucleotide array fixed to a surface and comprises the entire corresponding set of complementary sequences. Analysis of the level of each fluorescent molecular tag sequence is then determined to estimate the relative amount of growth of GRACE strain of the set, in those media, in the presence and absence of the compound tested.

Therefore, for each GRACE strain of the set tested, there could be, in one non-limiting example of this method, four values for the level of the corresponding molecular tag found within the surviving population. They would correspond to cell growth under repressing and non-repressing conditions, both in the presence and absence of the

compound being tested. Comparison of growth in the presence and absence of the test compound provides a value or "indicator" for each set of growth media; that is, an indicator derived under repressing and non-repressing conditions. Again, comparison of the two indicator values will reveal if the test compound is active against the gene product expressed by the modified allelic gene pair carried by that specific member of the GRACE set tested.

In still another aspect of the present invention, each potential drug target gene in this heterozygous tagged or bar-coded collection, may be overexpressed by subsequently introducing either the Tet promoter or another strong, constitutively expressed promoter (e. g. *CaACT1*, *CaADHI* and *CaPGK1*) upstream of the remaining non-disrupted allele. These constructions allow a further increase in the dosage of the encoded target gene product of individual essential genes to be used in mixed-population drug susceptibility studies. Although overexpression may itself disrupt the normal growth rate of numerous members of the population, reliable comparisons could still be made between mock and drug-treated mixed cultures to identify compound-specific growth differences.

In *S. cerevisiae*, the molecular drug targets of several well-characterized compounds including 3-amino-triazol, benomyl, tunicamycin and fluconazole were identified by a similar approach. In that study, bar-coded strains bearing heterozygous mutations in *HIS3*, *TUB1*, *ALG7*, and *ERG11*, (i.e. the respective drug targets to the compounds listed above) displayed significantly greater sensitivity when challenged with their respective compound than other heterozygote bar-coded strains when grown together in a mixed population.

In another aspect of the present invention, screens for antifungal compounds can be carried out using complex mixtures of compounds that comprise at least one compound active against the target strain. Tagging or bar-coding the GRACE strain collection facilitates a number of large scale analyses necessary to identify gene sets as well as evaluate and ultimately evaluate individual targets within particular gene sets. For example, mixed-population drug screening using a bar-coded GRACE strain collection effectively functions as a comprehensive whole cell assay. Minimal amounts of a complex compound library are sufficient to identify compounds that act on individual essential target genes within the collection. This is done without the need to array the collection. Also, strong predictions as to the 'richness' of any particular compound library could be made before committing to it in drug screening. It becomes possible then to assess whether, for example, a carbohydrate-based chemical library possesses greater fungicidal activity than a natural product or synthetic compound library. Particularly potent compounds within any complex library of molecules can be immediately identified and evaluated according to the

priority of targets and assays available for drug screening. Alternatively, the invention provides applying this information to developing "tailored" screens, in which only those targets which were demonstrated to be inactivated in mixed population experiments by a particular compound library would be included in subsequent array-formatted screens.

5 Traditionally, drug discovery programs have relied on an individual or a limited set of validated drug targets. The preceding examples emphasize that such an approach is no longer necessary and that high throughput target evaluation and drug screening are now possible. However, a directed approach based on selecting individual targets may still be preferred depending on the expertise, interest, strategy, or budget of a
10 drug discovery program.

5.5.3 Target Evaluation in an Animal Model System.

Currently, validation of an essential drug target is demonstrated by examining the effect of gene inactivation under standard laboratory conditions. Putative
15 drug target genes deemed nonessential under standard laboratory conditions may be examined within an animal model, for example, by testing the pathogenicity of a strain homozygous for a deletion in the target gene versus wild type. However, essential drug targets are precluded from animal model studies. Therefore, the most desirable drug targets are omitted from the most pertinent conditions to their target evaluation.

20 In an embodiment of the invention, conditional expression, provided by the GRACE essential strain collection, overcomes this longstanding limitation to target validation within a host environment. Animal studies can be performed using mice inoculated with GRACE essential strains and examining the effect of gene inactivation by conditional expression. In a preferred embodiment of the invention, the effect on mice
25 injected with a lethal inoculum of a GRACE essential strain could be determined depending on whether the mice were provided with an appropriate concentration of tetracycline to inactivate expression of a drug target gene. The lack of expression of a gene demonstrated to be essential under laboratory conditions can thus be correlated with prevention of a terminal *C. albicans* infection. In this type of experiment, only mice "treated" with
30 tetracycline-supplemented water, are predicted to survive infection because inactivation of the target gene has killed the GRACE strain pathogen within the host.

 In yet another embodiment of the invention, conditional expression could be achieved using a temperature-responsive promoter to regulate expression of the target gene or a temperature sensitive allele of a particular drug target, such that the gene is functional at
35 30°C but inactivated within the normal body temperature of the mouse.

In the same manner as described above for essential genes, it is equally feasible to demonstrate whether nonessential genes comprising the GRACE strain collection are required for pathogenicity in a mouse model system. Included in this set are multiple genes whose null phenotype results in a reduced growth rate and may attenuate the virulence of the pathogen. Many mutants demonstrating a slow growth phenotype may represent hypomorphic mutations in otherwise essential genes (as demonstrated by alternative methods) which are simply not completely inactivated by the conditional expression method used to construct the GRACE strain. One important use of such strains is to assess whether any given essential gene doubly functions in the process of virulence. Essential genes that display substantially reduced virulence and growth rate when only partially inactivated represent "multifactorial" drug targets for which even minimally inhibitory high specificity compounds would display therapeutic value. Collectively, all GRACE strains that fail to cause fungal infection in mice under conditions of gene inactivation by tetracycline (or alternative gene inactivation means) define a subset of genes that are required for pathogenicity, i.e., GRACE pathogenicity subset. More defined subsets of pathogenicity genes, for example those genes required for particular steps in pathogenesis (e.g. adherence or invasion) may be determined by applying the GRACE pathogenicity subset of strains to in vitro assays which measure the corresponding process. For example, examining GRACE pathogenicity strains in a buccal adhesion or macrophage assay by conditional expression of individual genes would identify those pathogenicity factors required for adherence or cell invasion respectively.

The GRACE strain collection or a desired subset thereof is also well suited for evaluating acquired resistance/suppression or distinguishing between fungicidal/fungistatic phenotypes for an inactivated drug target within an animal model system. In this embodiment of the invention, GRACE strains repressed for expression of different essential drug target genes would be inoculated into mice raised on tetracycline-supplemented water. Each of the GRACE strains would then be compared according to the frequency of death associated with the different mice populations they infected. It is expected that the majority of infected mice will remain healthy due to fungal cell death caused by tetracycline-dependent inactivation of the essential gene in the GRACE strain. However, a GRACE strain harboring a drug target more likely to develop extragenic suppressors because it is a fungistatic target rather than fungicidal one, or suppressed by an alternative physiological process active within a host environment, can be identified by the higher incidence of lethal infections detected in mice infected with this particular strain. By this method, it is possible to evaluate/rank the likelihood that individual drug target genes

may develop resistance within the host environment.

5.5.4 Rational Design of Binding Compounds

Compounds identified via assays such as those described herein can be useful, for example, for inhibiting the growth of the infectious agent and/or ameliorating the symptoms of an infection. Compounds can include, but are not limited to, other cellular proteins. Binding compounds can also include, but are not limited to, peptides such as, for example, soluble peptides, comprising, for example, extracellular portions of target gene product transmembrane receptors, and members of random peptide libraries (see, *e.g.*, Lam et al., 1991, *Nature* 354:82-84; Houghten et al., 1991, *Nature* 354:84-86) made of D-and/or L-configuration amino acids, rationally-designed antipeptide peptides, (see *e.g.*, Hurby *et al.*, Application of Synthetic Peptides: Antisense Peptides," In *Synthetic Peptides, A User's Guide*, W.H. Freeman, NY (1992), pp. 289-307), antibodies (including, but not limited to polyclonal, monoclonal, human, humanized, anti-idiotypic, chimeric or single chain antibodies, and FAb, F(ab')₂ and FAb expression library fragments, and epitope-binding fragments thereof), and small organic or inorganic molecules. In the case of receptor-type target molecules, such compounds can include organic molecules (*e.g.*, peptidomimetics) that bind to the ECD and either mimic the activity triggered by the natural ligand (*i.e.*, agonists); as well as peptides, antibodies or fragments thereof, and other organic compounds that mimic the ECD (or a portion thereof) and bind to a "neutralize" natural ligand.

Computer modeling and searching technologies permit identification of compounds, or the improvement of already identified compounds, that can modulate target gene expression or activity. Having identified such a compound or composition, the active sites or regions are preferably identified. In the case of compounds affecting receptor molecules, such active sites might typically be ligand binding sites, such as the interaction domains of ligand with receptor itself. The active site is identified using methods known in the art including, for example, from the amino acid sequences of peptides, from the nucleotide sequences of nucleic acids, or from study of complexes of the relevant compound or composition with its natural ligand. In the latter case, chemical or X-ray crystallographic methods are used to find the active site by finding where on the factor the complexed ligand is found.

The three-dimensional geometric structure of the active site is then preferably determined. This is done by known methods, including X-ray crystallography, which determines a complete molecular structure. Solid or liquid phase NMR is also used to determine certain intra-molecular distances within the active site and/or in the ligand

binding complex. Other experimental methods of structure determination known to those of skill in the art, are also used to obtain partial or complete geometric structures. The geometric structures are measured with a complexed ligand, natural or artificial, which increases the accuracy of the active site structure determined. Methods of computer based numerical modeling are used to complete the structure (*e.g.*, in embodiments wherein an incomplete or insufficiently accurate structure is determined) or to improve its accuracy.

Finally, having determined the structure of the active site, either experimentally, by modeling, or by a combination, candidate modulating compounds are identified by searching databases containing compounds along with information on their molecular structure. Such a search seeks compounds having structures that match the determined active site structure and that interact with the groups defining the active site. Such a search can be manual, but is preferably computer assisted. These compounds found from this search are potential target or pathway gene product modulating compounds.

Alternatively, these methods are used to identify improved modulating compounds from an already known modulating compound or ligand. The composition of the known compound is modified and the structural effects of modification are determined using the experimental and computer modeling methods described above applied to the new composition. The altered structure is then compared to the active site structure of the compound to determine if an improved fit or interaction results. In this manner systematic variations in composition, such as by varying side groups, are quickly evaluated to obtain modified modulating compounds or ligands of improved specificity or activity.

Further experimental and computer modeling methods useful to identify modulating compounds based upon identification of the active sites of target or pathway gene or gene products and related transduction and transcription factors are apparent to those of skill in the art.

There are a number of articles that review the art of computer modeling of drugs that interact with specific proteins, including the following: Rotivinen et al., 1988, *Acta Pharmaceutica Fennica* 97:159-166; Ripka, (June 16, 1988), *New Scientist* 54-57; McKinally and Rossmann, 1989, *Annu. Rev. Pharmacol. Toxicol.* 29:111-122; Perry and Davies, *OSAR: Quantitative Structure-Activity Relationships in Drug Design* pp. 189-193 (Alan R. Liss, Inc. 1989); Lewis and Dean, 1989 *Proc. R. Soc. Lond.* 236:125-140 and 1-162; and, with respect to a model receptor for nucleic acid components, Askew et al., 1989, *J. Am. Chem. Soc.* 111:1082-1090.

Although generally described above with reference to design and generation of compounds which could alter binding, one could also screen libraries of known

compounds, including natural products or synthetic chemicals, as well as other biologically active materials, including proteins, for compounds which are inhibitors or activators.

5.6 Transcriptional Profiling

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5.6.1 Analysis of Gene Expression

Gene expression profiling techniques are important tools for the identification of suitable biochemical targets, as well as for the determination of the mode of action of known compounds. Completion of the *C. albicans* genome sequence and development of nucleic acid microarrays incorporating this information, will enable genome-wide gene expression analyses to be carried out with this diploid pathogenic fungus. Therefore, the present invention provides methods for obtaining the transcriptional response profiles for both essential and virulence/pathogenicity genes of *Candida albicans*. Conditional expression of essential genes serves to delineate, for example, regulatory interactions valuable for the design of drug screening programs focused upon *C. albicans*.

In an embodiment of the present invention, the GRACE strain collection is used for the analysis of expression of essential genes within this pathogen. One particularly powerful application of such a strain collection involves the construction of a comprehensive transcriptional profile database for the entire essential gene set or a desired subset of essential genes within a pathogen. Such a database is used to compare the response profile characteristic of lead antimycotic compounds with the profile obtained with new anti-fungal compounds to distinguish those with similar from those with distinct modes of action. Matching (or even partially overlapping) the transcriptional response profiles determined after treatment of the strain with the lead compound with that obtained with a particular essential target gene under repressing conditions, is used to identity the target and possible mode of action of the drug.

Gene expression analysis of essential genes also permits the biological function and regulation of those genes to be examined within the pathogen, and this information is incorporated within a drug screening program. For example, transcriptional profiling of essential drug targets in *C. albicans* permits the identification of novel drug targets which participate in the same cellular process or pathway uncovered for the existing drug target and which could not otherwise be identified without direct experimentation within the pathogen. These include genes not only unique to the pathogen but also broad-range gene classes possessing a distinct function or subject to different regulation in the pathogen. Furthermore, pathogen-specific pathways may be uncovered and exploited for

the first time.

In another aspect of the present invention, the gene expression profile of GRACE-derived strains under nonrepressing or induced conditions is established to evaluate the overexpression response profile for one or more drug targets. For example, overexpression of genes functioning in signal transduction pathways often display unregulated activation of the pathway under such conditions. Moreover, several signaling pathways have been demonstrated to function in the pathogenesis process. Transcriptional response profiles generated by overexpressing *C. albicans* GRACE strains provide information concerning the set of genes regulated by such pathways; any of which may potentially serve an essential role in pathogenesis and therefore representing promising drug targets. Furthermore, analysis of the expression profile may reveal one or more genes whose expression is critical to the subsequent expression of an entire regulatory cascade. Accordingly, these genes are particularly important targets for drug discovery and mutants carrying the corresponding modified allelic pair of genes form the basis of a mechanism-of-action based screening assays. Presently such an approach is not possible. Current drug discovery practices result in an exceedingly large number of "candidate" compounds and little understanding of their mode of action. A transcriptional response database comprising both gene shut-off and overexpression profiles generated using the GRACE strain collection offers a solution to this drug discovery bottleneck by 1) determining the transcriptional response or profile resulting from an antifungal's inhibition of a wild type strain, and 2) comparing this response to the transcriptional profiles resulting from inactivation or overexpression of drug targets comprising the GRACE strain collection.

Matching or significantly correlating transcriptional profiles resulting from both genetic alteration of a drug target and chemical/compound inhibition of wild type cells provides evidence linking the compound to its cellular drug target and suggests its mechanism of action.

Accordingly, the invention provides a method for evaluating a compound against a target gene product encoded by a nucleotide sequence comprising one of SEQ ID NO: 1 to 61, said method comprising the steps of (a) contacting wild type diploid fungal cells or control cells with the compound and generating a first transcription profile; (b) determining the transcription profile of mutant diploid fungal cells, such as a GRACE strain, which have been cultured under conditions wherein the second allele of the target gene is substantially underexpressed, not expressed or overexpressed and generating a second transcription profile for the cultured cells; and comparing the first transcription

profile with the second transcription profile to identify similarities in the profiles. For comparisons, similarities of profiles can be expressed as an indicator value; and the higher the indicator value, the more desirable is the compound.

5 5.6.2 Identification of Secondary Targets

Methods are described herein for the identification of secondary targets.

"Secondary target," as used herein, refers to a gene whose gene product exhibits the ability to interact with target gene products involved in the growth and/or survival of an organism (i.e., target essential gene products), under a set of defined conditions, or in the pathogenic mechanism of the organism, (i.e., target virulence gene products) during infection of a host.

Any method suitable for detecting protein-protein interactions can be employed for identifying secondary target gene products by identifying interactions between gene products and target gene products. Such known gene products can be cellular or extracellular proteins. Those gene products which interact with such known gene products represent secondary target gene products and the genes which encode them represent secondary targets.

Among the traditional methods employed are co-immunoprecipitation, crosslinking and co-purification through gradients or chromatographic columns. Utilizing procedures such as these allows for the identification of secondary target gene products. Once identified, a secondary target gene product is used, in conjunction with standard techniques, to identify its corresponding secondary target. For example, at least a portion of the amino acid sequence of the secondary target gene product is ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique (see, *e.g.*, Creighton, 1983, "Proteins: Structures and Molecular Principles," W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained can be used as a guide for the generation of oligonucleotide mixtures that can be used to screen for secondary target gene sequences. Screening can be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and for screening are well-known. (See, *e.g.*, Ausubel, *supra.*, and PCR Protocols: A Guide to Methods and Applications, 1990, Innis, M. et al., eds. Academic Press, Inc., New York).

Additionally, methods are employed which result in the simultaneous identification of secondary targets which encode proteins interacting with a protein involved in the growth and/or survival of an organism under a set of defined conditions, or in the pathogenic mechanism of the organism during infection of a host. These methods include,

for example, probing expression libraries with labeled primary target gene protein known or suggested to be involved in or critical to these mechanisms, using this protein in a manner similar to the well known technique of antibody probing of λ gt11 phage libraries.

One method which detects protein interactions in vivo, the two-hybrid
5 system, is described in detail for illustration purposes only and not by way of limitation. One version of this system has been described (Chien et al., 1991, Proc. Natl. Acad. Sci. USA, 88:9578-9582) and is commercially available from Clontech (Palo Alto, CA).

Briefly, utilizing such a system, plasmids are constructed that encode two
hybrid proteins: one consists of the DNA-binding domain of a transcription activator protein
10 fused to a known protein, in this case, a protein known to be involved in growth of the organism, or in pathogenicity, and the other consists of the activator protein's activation domain fused to an unknown protein that is encoded by a cDNA which has been recombined into this plasmid as part of a cDNA library. The plasmids are transformed into a strain of the yeast *S. cerevisiae* that contains a reporter gene (e.g., *lacZ*) whose regulatory
15 region contains the transcription activator's binding sites. Either hybrid protein alone cannot activate transcription of the reporter gene, the DNA-binding domain hybrid cannot because it does not provide activation function, and the activation domain hybrid cannot because it cannot localize to the activator's binding sites. Interaction of the two hybrid proteins reconstitutes the functional activator protein and results in expression of the reporter gene,
20 which is detected by an assay for the reporter gene product.

The two-hybrid system or related methodology is used to screen activation domain libraries for proteins that interact with a known "bait" gene product. By way of example, and not by way of limitation, target essential gene products and target virulence gene products are used as the bait gene products. Total genomic or cDNA sequences
25 encoding the target essential gene product, target virulence gene product, or portions thereof, are fused to the DNA encoding an activation domain. This library and a plasmid encoding a hybrid of the bait gene product fused to the DNA-binding domain are cotransformed into a yeast reporter strain, and the resulting transformants are screened for those that express the reporter gene. For example, and not by way of limitation, the bait
30 gene is cloned into a vector such that it is translationally fused to the DNA encoding the DNA-binding domain of the GAL4 protein. These colonies are purified and the library plasmids responsible for reporter gene expression are isolated. DNA sequencing is then used to identify the proteins encoded by the library plasmids.

A cDNA library of the cell line from which proteins that interact with bait
35 gene product are to be detected is made using methods routinely practiced in the art.

According to the particular system described herein, for example, the cDNA fragments are inserted into a vector such that they are translationally fused to the activation domain of GAL4. This library is co-transformed along with the bait gene-GAL4 fusion plasmid into a yeast strain which contains a lacZ gene driven by a promoter which contains GAL4
5 activation sequence. A cDNA encoded protein, fused to GAL4 activation domain, that interacts with bait gene product reconstitutes an active GAL4 protein and thereby drive expression of the lacZ gene. Colonies which express lacZ are detected by their blue color in the presence of X-gal. The cDNA can then be purified from these strains, and used to
10 produce and isolate the bait gene-interacting protein using techniques routinely practiced in the art.

Once a secondary target has been identified and isolated, it is further characterized and used in drug discovery by the methods of the invention.

5.6.3 Use of Gene Expression Arrays

15 To carry out profiling, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass surface, silicon, nylon membrane, or the like. Such arrays are used by researchers to quantify relative gene expression under different conditions. An example of this technology is found in U.S. Patent No. 5807522, which is hereby
20 incorporated by reference.

It is possible to study the expression of substantially all of the genes in the genome of a particular microbial organism using a single array. For example, the arrays may consist of 12 x 24 cm nylon filters containing PCR products corresponding to ORFs from *Candida albicans*. 10 ngs of each PCR product are spotted every 1.5 mm on the filter.
25 Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or amplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation. Quantitative analysis is done using a phosphorimager.

Hybridization of cDNA made from a sample of total cell mRNA to such an
30 array followed by detection of binding by one or more of various techniques known to those in the art provides a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows
35 for a comparison of the relative amount of expression of each individual gene during growth

under the different conditions.

Gene expression arrays are used to analyze the total mRNA expression pattern at various time points after reduction in the level or activity of a gene product required for fungal proliferation, virulence or pathogenicity. Reduction of the level or activity of the gene product is accomplished by growing a GRACE strain under conditions in which the product of the nucleic acid linked to the regulatable promoter is rate limiting for fungal growth, survival, proliferation, virulence or pathogenicity or by contacting the cells with an agent which reduces the level or activity of the target gene product. Analysis of the expression pattern indicated by hybridization to the array provides information on other genes whose expression is influenced by reduction in the level or activity of the gene product. For example, levels of other mRNAs may be observed to increase, decrease or stay the same following reduction in the level or activity of the gene product required for growth, survival, proliferation, virulence or pathogenicity. Thus, the mRNA expression pattern observed following reduction in the level or activity of a gene product required for growth, survival, proliferation, virulence or pathogenicity identifies other nucleic acids required for growth, survival, proliferation, virulence or pathogenicity. In addition, the mRNA expression patterns observed when the fungi are exposed to candidate drug compounds or known antibiotics are compared to those observed when the level or activity of a gene product required for fungal growth, survival, proliferation, virulence or pathogenicity is reduced. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed when the level of the gene product is reduced, the drug compound is a promising therapeutic candidate. Thus, the assay is useful in assisting in the selection of promising candidate drug compounds for use in drug development.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different microorganisms, gene expression identify homologous genes in the two microorganisms.

5.7 Proteomics Assays

In another embodiment of the present invention, and in much the same way that the GRACE strain collection enables transcriptional profiling within a pathogen, a GRACE strain collection provides an invaluable resource for the analysis of the expressed protein complement of a genome. By evaluating the overall protein expression by members of a GRACE strain collection under repressing and non-repressing growth conditions, a correlation between the pattern of protein expression of a cell can be made with the non-expression or the level of expression of an essential gene. Accordingly, the invention

provides a pattern of expression of a set of proteins in a GRACE strain as determined by methods well known in the art for establishing a protein expression pattern, such as two-dimensional gel electrophoresis. A pluralities of protein expression patterns will be generated for a GRACE strain when the strain is cultured under different conditions and
5 different levels of expression of one of the modified allele.

In yet another embodiment, defined genetic mutations can be constructed to create strains exhibiting protein expression profiles comparable to those observed upon treatment of the strain with a previously uncharacterized compound. In this way, it is possible to distinguish between antimycotic compounds that act on multiple targets in a
10 complicated manner from other potential lead compounds that act on unique fungal-specific targets and whose mode of action can be determined.

Evaluation of the full complement of proteins expressed within a cell depends upon definitive identification of all protein species detectable on two-dimensional polyacrylamide gels or by other separation techniques. However, a significant fraction of
15 these proteins are of lower abundance and fall below the threshold level required for positive identification by peptide sequencing or mass spectrometry. Nevertheless, these "orphan" proteins are detectable using an analysis of protein expression by individual GRACE strains. Conditional expression of low abundance gene products facilitates their positive identification by comparing protein profiles of GRACE strains under repressing
20 *versus* nonrepressing or overexpression conditions. In some cases, a more complex protein profile results because of changes of steady state levels for multiple proteins, which is caused indirectly by manipulating the low abundance gene in question. Overexpression of individual targets within the GRACE strain collection can also directly aid orphan protein identification by providing sufficient material for peptide sequencing or mass spectrometry.

25 In various embodiments, the present invention provides a method of quantitative analysis of the expressed protein complement of a diploid pathogenic fungal cell: a first protein expression profile is developed for a control diploid pathogenic fungus, which has two, unmodified alleles for the target gene. Mutants of the control strain, in which one allele of the target gene is inactivated, for example, in a GRACE strain, by
30 insertion by or replacement with a disruption cassette, is generated. The other allele is modified such that expression of that second allele is under the control of a heterologous regulated promoter. A second protein expression profile is developed for this mutant fungus, under conditions where the second allele is substantially overexpressed as compared to the expression of the two alleles of the gene in the control strain. Similarly, if desired, a
35 third protein expression profile is developed, under conditions where the second allele is

substantially underexpressed as compared to the expression of the two alleles of the gene in the control strain. The first protein expression profile is then compared with the second expression profile, and if applicable, a third protein expression profile to identify an expressed protein detected at a higher level in the second profile, and if applicable, at a lower level in the third profile, as compared to the level in first profile.

Accordingly, the invention provides a method for evaluating a compound against a target gene product encoded by a nucleotide sequence comprising one of SEQ ID NO: 1 to 61, said method comprising the steps of (a) contacting wild type diploid fungal cells or control cells with the compound and generating a first protein expression profile; (b) determining the protein expression profile of mutant diploid fungal cells, such as a GRACE strain, which have been cultured under conditions wherein the second allele of the target gene is substantially underexpressed, not expressed or overexpressed and generating a second protein expression profile for the cultured cells; and comparing the first protein expression profile with the second protein expression profile to identify similarities in the profiles. For comparisons, similarities of profiles can be expressed as an indicator value; and the higher the indicator value, the more desirable is the compound.

5.8 Pharmaceutical Compositions And Uses Thereof

Compounds including nucleic acid molecules that are identified by the methods of the invention as described herein can be administered to a subject at therapeutically effective doses to treat or prevent infections by a pathogenic organism, such as *Candida albicans*. Depending on the target, the compounds may also be useful for treatment of a non-infectious disease in a subject, such as but not limited to, cancer. A therapeutically effective dose refers to that amount of a compound (including nucleic acid molecules) sufficient to result in a healthful benefit in the treated subject. Typically, but not so limited, the compounds act by reducing the activity or level of a gene product encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1 to 62. The subject to be treated can be a plant, a vertebrate, a mammal, an avian, or a human. These compounds can also be used for preventing or containing contamination of an object by *Candida albicans*, or used for preventing or inhibiting formation on a surface of a biofilm comprising *Candida albicans*. Biofilm comprising *C. albicans* are found on surfaces of medical devices, such as but not limited to surgical tools, implanted devices, catheters and stents.

5.8.1 Effective Dose

Toxicity and therapeutic efficacy of compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography. A useful dosage can range from 0.001 mg/kg body weight to 10 mg/kg body weight.

5.8.2 Formulations and Use

Pharmaceutical compositions for use in accordance with the present invention can be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus, the compounds and their physiologically acceptable salts and solvents can be formulated for administration by inhalation or insufflation (either through the mouth or the nose) or oral, buccal, parenteral or rectal administration.

For oral administration, the pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium

stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration can be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions can take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration (i.e., intravenous or intramuscular) by injection, via, for example, bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also

be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

6. EXAMPLES

6.1 Construction of a GRACE strain containing modified alleles of *CaKRE9*

Oligonucleotide primers for PCR amplification of the SAT selectable marker used in Step 1 (i.e. gene replacement) contain 25 nucleotides complementary to the SAT disruption cassette in pRC18-ASP, and 65 nucleotides homologous to regions flanking the *CaKRE9* open reading frame. Figure 2 illustrates the 2.2 kb *cakre9Δ::SAT* disruption fragment produced after PCR amplification and resulting gene replacement of the first wild type *CaKRE9* allele via homologous recombination following transformation. PCR conditions were as follows: 5-50 ng pRC18-ASP, 100 pmol of each primer, 200 μM dNTPs, 10 mM Tris- pH 8.3, 1.5 mM MgCl₂, 50 mM KCl, 1 unit Taq DNA polymerase (Gibco). PCR amplification times were: 5 min 94°C, 1 min 54°C, 2 min 72°C, for 1 cycle; 45 sec 94°C, 45 sec 54°C, 2 min 72°C, for 30 cycles. Transformation was performed using the lithium acetate method adapted for *C. albicans*, by Braun and Johnson, (Braun, B. R., and A. D. Johnson (1997), Control of filament formation in *Candida albicans* by the transcriptional repressor TUP1, Science 277:105-109), with minor modifications, including shorter incubation times at 30°C and 42°C (1 hr and 5 min respectively) and a greater amount of material transformed (50 μg of ethanol-precipitated *cakre9Δ::SAT* PCR product). Transformed cells were spread onto YPD plates and incubated overnight at 30°C, providing a preincubation period for expression of SAT prior to replica plating onto YPD medium containing streptothricin (400μg/ml). Streptothricin-resistant colonies were detected after 36 hr and *cakre9Δ::SAT/CaKRE9* heterozygotes identified by PCR analysis using suitable primers which amplify both *CaKRE9* and *cakre9Δ::SAT* alleles.

Oligonucleotide primers for PCR amplification of the conditional promoter used in Step 2 (i.e. promoter replacement) contain 25 nucleotides complementary to the *CaHIS3*-marked tetracycline regulated promoter cassette in pBSK-HT4 and 65 nucleotides of homologous sequence corresponding to promoter regions -270 to -205, relative to the point of transcription initiation, and nucleotides 1-65 of the *CaKRE9* open reading frame.

The resulting 2.2 kb PCR product was transformed into the *cakre9Δ::SAT/CaKRE9* heterozygous strain produced in step 1, and His⁺ transformants selected on YNB agar. Bonafide *CaKRE9* GRACE strains containing both a *cakre9Δ::SAT* allele and *CaHIS3-Tet-CaKRE9* allele were determined by PCR analysis. Typically, 2 independent GRACE strains
5 are constructed and evaluated to provide a reliable determination of the terminal phenotype of any given drug target. Terminal phenotype is that phenotype caused by the absence of the gene product of an essential gene

6.2 Phenotype determination of the *CaKRE9* Grace strain

The terminal phenotype of the resulting GRACE strains was evaluated in three independent methods. In the first, rapid determination of the *CaKRE9* GRACE strain terminal phenotype was achieved by streaking approximately 1.0×10^6 cells onto both a YNB plate and YNB plate containing 100 μg/ml tetracycline and comparing growth rate
15 after 48 hr at room temperature. For essential genes, such as *CaKRE9*, no significant growth is detected in the presence of tetracycline. In the second approach, the essential nature of a gene may be determined by streaking *CaKRE9* GRACE cells onto a casamino acid plate containing 625 μg/ml 5-fluoroorotic acid (5FOA) and 100 μg/ml uridine to select for ura⁻ cells which have excised (*via* recombination between *CaLEU2* sequence duplications
20 created during targeted integration) the transactivator gene that is normally required for expression of the tetracycline promoter-regulated target gene. Again, whereas nonessential GRACE strains demonstrate robust growth under such conditions, essential GRACE strains fail to grow. Quantitative evaluation of the terminal phenotype associated with an essential GRACE strain is performed using 2×10^3 cells/ml of overnight culture inoculated into 5.0
25 ml YNB either lacking or supplemented with 100 μg/ml tetracycline and measuring optical density (O.D.₆₀₀) after 24 and 48 hr incubation at 30°C. Typically, for essential GRACE strains, no significant increase in optical density is detected after 48 hrs. Discrimination between cell death (cidal) and growth inhibitory (static) terminal phenotypes for a demonstrated essential gene is achieved by determining the percentage of viable cells (as
30 judged by the number of colony forming units (CFU) from an equivalent of 2×10^3 washed cells at T=0) from the above tetracycline-treated cultures after 24 and 48 hours of incubation. Essential GRACE strains producing a cidal terminal phenotype are those which display a reduction in percent viable cells (i.e. $< 2 \times 10^3$ CFU) following incubation under repressing conditions.

6.3 Target Level Variation in Whole Cell Assays

In order to demonstrate the utility of target level expression in whole cell assays for drug screening, both a *CaHIS3* heterozygote strain and a tetracycline promoter-regulated *CaHIS3* GRACE strain were compared against a wild type (diploid) *CaHIS3* strain for sensitivity towards the 3-aminotriazole (3-AT) (Fig. 6). 3-AT is a competitive inhibitor of the enzyme encoded by *CaHIS3*, imidazoleglycerol phosphate dehydratase, and together serve as a model for a drug and drug target respectively. Overexpression, achieved by the constitutive expression level of *CaHIS3* maintained by the tetracycline promoter, confers 3-AT resistance at concentrations sufficient to completely inhibit growth of both wild type and *CaHIS3* heterozygote strains (Fig 6A). The phenotype observed is consistent with that expected in light of the predicted 7.5 fold overexpression of *CaHIS3* determined by Northern blot analysis (see Fig 5). A heterozygous *CaHIS3* strain demonstrates enhanced sensitivity (i.e. haploinsufficient phenotype) to an intermediate 3-AT concentration unable to effect either wild type or tetracycline promoter-based overproducing *CaHIS3* strains noticeably (Fig 6B). A third *CaHIS3* expression level evaluated for differential sensitivity to 3-AT was produced by partial repression of the GRACE *CaHIS3* strain using a threshold concentration of tetracycline 0.1% that normally is used to achieve complete shut-off.

This level of *CaHIS3* expression represents the minimum expression level required for viability and as predicted, demonstrates an enhanced drug sensitivity relative the heterozygous *CaHIS3* strain at an intermediate 3-AT concentration (Fig 6C). Similarly, GRACE strain-specific drug resistance and sensitivity phenotypes to fluconazole and tunicamycin have been demonstrated by increasing and decreasing the level of expression of their respective known drug targets, *CaERG11* and *CaALG7*. Together these results demonstrate that three different levels of expression are achieved using the *C. albicans* GRACE strain collection, and that they exhibit the predicted drug sensitivity phenotypes between known drugs and their known drug target. Moreover, these experiments clearly indicate how distinct levels of target gene products synthesized within the pathogen could be directly applied in whole cell assay based drug screens to identify novel antifungal compounds against those novel drug targets validated using the GRACE method.

6.4 Identification of a Target Pathway

A target pathway is a genetic or biochemical pathway wherein one or more of the components of the pathway (e.g., enzymes, signaling molecules, etc) is a drug target as determined by the methods of the invention.

6.4.1. Preparation of Stocks of GRACE Strains for Assay

To provide a consistent source of cells to screen, frozen stocks of host GRACE strains are prepared using standard microbiological techniques. For example, a single clone of the microorganism can be isolated by streaking out a sample of the original stock onto an agar plate containing nutrients for cell growth and an antibiotic for which the GRACE strain contains a gene which confers resistance. After overnight growth an isolated colony is picked from the plate with a sterile needle and transferred to an appropriate liquid growth medium containing the antibiotic to which the GRACE strain is resistant. The cells are incubated under appropriate growth conditions to yield a culture in exponential growth. Cells are frozen using standard techniques.

6.4.2. Growth of GRACE Strains for Use in the Assay

Prior to performing an assay, a stock vial is removed from the freezer, rapidly thawed and a loop of culture is streaked out on an agar plate containing nutrients for cell growth and an antibiotic for which the GRACE strain contains a gene which confers resistance. After overnight growth, randomly chosen, isolated colonies are transferred from the plate (sterile inoculum loop) to a sterile tube containing medium containing the antibiotic to which the GRACE strain contains a gene which confers resistance. After vigorous mixing to form a homogeneous cell suspension, the optical density of the suspension is measured and if necessary an aliquot of the suspension is diluted into a second tube of medium plus antibiotic. The culture is then incubated until the cells reach an optical density suitable for use in the assay.

6.4.3. Selection of Medium to be Used in Assay

Two-fold dilution series of the inducer or repressor for the regulatable promoter which is linked to the gene required for the fungal proliferation, virulence or pathogenicity of the GRACE strain are generated in culture medium containing the appropriate antibiotic for which the GRACE strain contains a gene which confers resistance. Several medium are tested side by side and three to four wells are used to evaluate the effects of the inducer or repressor at each concentration in each media. Equal volumes of test media-inducer or repressor and GRACE cells are added to the wells of a 384 well microtiter plate and mixed. The cells are prepared as described above and diluted in the appropriate medium containing the test antibiotic immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells of each medium

that do not contain inducer or repressor. Cell growth is monitored continuously by incubation by monitoring the optical density of the wells. The percent inhibition of growth produced by each concentration of inducer or repressor is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in medium without inducer or repressor. The medium yielding greatest sensitivity to inducer or repressor is selected for use in the assays described below.

6.4.4. Measurement of Test Antibiotic Sensitivity in GRACE Strains in which the Level of the Target Gene Product is not Rate Limiting

Two-fold dilution series of antibiotics of known mechanism of action are generated in the culture medium selected for further assay development that has been supplemented with the antibiotic used to maintain the GRACE strain. A panel of test antibiotics known to act on different pathways is tested side by side with three to four wells being used to evaluate the effect of a test antibiotic on cell growth at each concentration. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the medium selected for assay development supplemented with the antibiotic required to maintain the GRACE strain and are diluted in identical medium immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells that lack antibiotic, but contain the solvent used to dissolve the antibiotics. Cell growth is monitored continuously by incubation in a microtiter plate reader monitoring the optical density of the wells. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in medium without antibiotic. A plot of percent inhibition against log [antibiotic concentration] allows extrapolation of an IC_{50} value for each antibiotic.

6.4.5. Measurement of Test Antibiotic Sensitivity in the GRACE Strains in which the Level of the Target Gene Product is Rate Limiting

The culture medium selected for use in the assay is supplemented with inducer or repressor at concentrations shown to inhibit cell growth by a desired amount as described above, as well as the antibiotic used to maintain the GRACE strain. Two fold dilution series of the panel of test antibiotics used above are generated in each of these media. Several antibiotics are tested side by side in each medium with three to four wells being used to evaluate the effects of an antibiotic on cell growth at each concentration.

Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the medium selected for use in the assay supplemented with the antibiotic required to maintain the GRACE strain. The cells are diluted 1:100 into two aliquots of identical medium containing concentrations of inducer that have been shown to inhibit cell growth by the desired amount and incubated under appropriate growth conditions. Immediately prior to addition to the microtiter plate wells, the cultures are adjusted to an appropriate optical density by dilution into warm sterile medium supplemented with identical concentrations of the inducer and antibiotic used to maintain the GRACE strain. For a control, cells are also added to several wells that contain solvent used to dissolve test antibiotics but which contain no antibiotic. Cell growth is monitored continuously by incubation under suitable growth conditions in a microtiter plate reader monitoring the optical density of the wells. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in medium without antibiotic. A plot of percent inhibition against log [antibiotic concentration] allows extrapolation of an IC_{50} value for each antibiotic.

6.4.6. Determining the Specificity of the Test Antibiotics

A comparison of the IC_{50} s generated by antibiotics of known mechanism of action under conditions in which the level of the gene product required for fungal proliferation, virulence or pathogenicity is rate limiting or is not rate limiting allows the pathway in which a gene product required for fungal proliferation, virulence or pathogenicity lies to be identified. If cells expressing a rate limiting level of a gene product required for fungal proliferation, virulence or pathogenicity are selectively sensitive to an antibiotic acting via a particular pathway, then the gene product encoded by the gene linked to the regulatable promoter in the GRACE strain is involved in the pathway on which the antibiotic acts.

6.4.7. Identification of Pathway in which a Test Antibiotic Acts

As discussed above, the cell-based assay may also be used to determine the pathway against which a test antibiotic acts. In such an analysis, the pathways against in which the gene under the control of the regulatable promoter in each member of a panel of GRACE strains lies is identified as described above. A panel of cells, each containing a regulatable promoter which directs transcription of a proliferation, virulence or pathogenicity-required nucleic acid which lies in a known biological pathway required for

5 fungal proliferation, virulence or pathogenicity, is contacted with a test antibiotic for which it is desired to determine the pathway on which it acts under conditions in which the gene product of the nucleic acid is rate limiting or is not rate limiting. If heightened sensitivity is observed in cells in which the gene product is rate limiting for a gene product which lies in a particular pathway but not in cells expressing rate limiting levels of gene products which lie in other pathways, then the test antibiotic acts against the pathway for which heightened sensitivity was observed.

10 The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

15 Various references are cited herein, the disclosures of which are incorporated by reference in their entireties.

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What is claimed is:

1. A method for constructing a strain of diploid fungal cells in which
5 both alleles of a gene are modified, the method comprising the steps of:
 - (a) modifying a first allele of a gene in diploid fungal cells by recombination using a gene disruption cassette comprising a first nucleotide sequence encoding an expressible selectable marker, thereby providing heterozygous diploid fungal cells in which the first allele of the gene is inactivated; and
 - 10 (b) modifying the second allele of the gene in the heterozygous diploid fungal cells by recombination using a promoter replacement fragment comprising a second nucleotide sequence encoding a heterologous promoter, such that expression of the second allele of the gene is regulated by the heterologous promoter.
- 15 2. A method of assembling a collection of diploid fungal cells each of which comprises modified alleles of a different gene, the method comprising the steps of:
 - (a) modifying a first allele of a first gene in diploid fungal cells by recombination using a gene disruption cassette comprising a first nucleotide sequence encoding an expressible selectable marker, thereby providing heterozygous diploid fungal
20 cells in which the first allele of the gene is inactivated;
 - (b) modifying a second allele of the first gene in the heterozygous diploid fungal cells by recombination using a promoter replacement fragment comprising a second nucleotide sequence encoding a heterologous promoter, such that expression of the second allele of the gene is regulated by the heterologous promoter, thereby providing a first
25 strain of diploid fungal cells comprising a modified allelic pair of the first gene; and
 - (c) repeating steps (a) and (b) a plurality of times, wherein a different gene is modified with each repetition, thereby providing the collection of diploid fungal cells each comprising the modified alleles of a different gene.
- 30 3. The method of claim 1 or 2, wherein the selectable marker in the gene disruption cassette is disposed between a first region and a second region, wherein the first region and the second region hybridize separately to non-contiguous regions of the first allele of the gene in the diploid fungal cells.
- 35 4. The method of claim 3, wherein the selectable marker is selected

from the group consisting of CaSAT1, CaBSR1, CaURA3, CaHIS3, CaLEU2, CaTRP1, and combinations thereof.

5. The method of claim 1, wherein the diploid fungal cells are cells of
5 fungal species selected from the group consisting of *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavis*, *Candida albicans*, *Candida tropicalis*, *Candida parapsilopsis*, *Candida krusei*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Exophiala dermatitidis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Pneumocystis carinii*, *Trichosporon beigelii*, *Rhizopus arrhizus*, *Mucor rouxii*, *Rhizomucor pusillus*, *Absidia corymbigera*,
10 *Botrytis cinerea*, *Erysiphe graminis*, *Magnaporthe grisea*, *Puccinia recodita*, *Septoria triticii*, *Tilletia controversa*, and *Ustilago maydis*.

6. The method of claim 1, wherein the diploid fungal cells are cells of
15 *Candida*.

7. The method of claim 1 or 2, wherein the method further comprises
(c) introducing a nucleotide sequence encoding a transactivation
fusion protein that is expressible in the diploid fungal cell, said transactivation fusion
protein comprising a DNA binding domain and a transcription activation domain; and
20 wherein the heterologous promoter in the promoter replacement fragment comprises at least
one copy of a nucleotide sequence which is bound by the DNA binding domain of the
transactivation fusion protein, such that binding of the transactivation fusion protein
increases transcription from the heterologous promoter.

25 8. The method of claim 7, wherein the promoter replacement fragment
further comprises a selectable marker.

9. The method of claim 8, wherein the selectable marker is selected
30 from the group consisting of CaHIS3, CaSAT1, CaBSR1, CaURA3, CaLEU2, CaTRP1,
and combinations thereof.

10. A strain of diploid fungal cells comprising modified alleles of a gene,
wherein the first allele of the gene is inactivated by recombination using a gene disruption
35 cassette comprising a nucleotide sequence encoding an expressible selectable marker; and
the expression of the second allele of the gene is regulated by a heterologous promoter that

is operably linked to the coding region of the second allele of the gene.

11. The diploid fungal cells of claim 10 further comprising a nucleotide sequence encoding a transactivation fusion protein that is expressible in the diploid fungal cell, said transactivation fusion protein comprising a DNA binding domain and a transcription activation domain; and wherein the heterologous promoter in the promoter replacement fragment comprises at least one copy of a nucleotide sequence which is bound by the DNA binding domain of the transactivation fusion protein, such that binding of the transactivation fusion protein increases transcription from the heterologous promoter.

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12. The strain of diploid fungal cells of claim 10 or 11, wherein the gene is a gene essential for the growth and/or survival of the cells.

13. The strain of diploid fungal cells of claim 10 or 11, wherein the gene is a gene that contributes to the virulence and/or pathogenicity of the fungal cells against a host organism.

14. A collection of diploid fungal strains of claim 10 wherein each strain comprises modified alleles of a different gene, and wherein substantially all the different genes in the genome of the fungus are modified and represented in the collection.

15. A collection of diploid fungal strains of claim 10 each comprising the modified alleles of a different gene, wherein each gene is essential for the growth and/or survival of the cells.

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16. The collection of diploid fungal strains of claim 15, wherein substantially all of the essential genes in the genome of the pathogenic fungus are modified and present in the collection.

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17. A collection of diploid fungal strains of claim 10 each strain comprising the modified alleles of a different gene, wherein each gene contributes to the virulence and/or pathogenicity of the cells to a host organism.

18. The collection of diploid fungal strains of claim 17, wherein substantially all of the genes in the genome of the diploid fungus that contribute to the

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virulence and/or pathogenicity of the fungal cells against a host organism are modified and present in the collection.

19. The collection of diploid fungal strains of claim 14, wherein the
5 essential genes present in the collection all share a characteristic selected from the group consisting of: similar biological activity, similar intracellular localization, structural homology, sequence homology, distal terminal phenotype, static terminal phenotype, sequence homology to human genes, and exclusivity with respect to the organism.

10 20. The collection of claim 14, 15, 17, or 19 wherein the cells of each strain further comprise a molecular tag of about 20 nucleotides, the sequence of which is unique to each strain.

15 21. The collection of claim 20, wherein the molecular tag is disposed within the gene disruption cassette.

22. A nucleic acid molecule microarray comprising a plurality of nucleic acid molecules, wherein each nucleic acid molecule comprises a nucleotide sequence that is hybridizable to a target nucleotide sequence selected from the group consisting of SEQ ID
20 NO:1 through to SEQ ID NO:62.

23. A nucleic acid molecule microarray comprising a plurality of nucleic acid molecules, wherein each nucleic acid molecule comprises a nucleotide sequence that is hybridizable to the nucleotide sequence of a gene that is either essential to the growth of a
25 diploid fungal cell or contributes to the virulence and/or pathogenicity of the diploid fungal cells against a host organism.

24. A method for identifying a gene that is essential to the survival of a
30 fungus comprising the steps of:

- (a) culturing the diploid fungal cells of claim 10 under conditions wherein the second allele of the gene is substantially underexpressed or not expressed; and
- (b) determining viability of the cells; whereby a loss or reduction of viability as compared to a control indicates that the modified gene is essential to the survival
35 of the fungus.

25. A method for identifying a gene that is essential to the growth of a fungus comprising the steps of:

(a) culturing the diploid fungal cells of claim 10 under conditions wherein the second allele of the gene is substantially underexpressed or not expressed; and

5 (b) determining growth of the cells; whereby a loss or reduction of growth of the cells as compared to a control indicates that the modified gene is essential to the growth of the fungus.

26. A method for identifying a gene that contributes to the virulence and/or pathogenicity of a fungus comprising the steps of:

(a) culturing diploid fungal cells of claim 10 or 11 under conditions wherein the second allele of the gene is substantially underexpressed or not expressed; and

15 (b) determining the virulence and/or pathogenicity of the cells toward a host cell or organism; whereby a reduction of virulence and/or pathogenicity as compared to a control indicates that the modified gene contributes to the virulence and/or pathogenicity of the fungus.

27. A method for identifying a gene that contributes to the resistance of a diploid fungus to an antifungal agent comprising the steps of:

(a) culturing the diploid fungal cells of claim 10 under conditions wherein the second allele is substantially overexpressed and in the presence of the antifungal agent; and

25 (b) determining the viability of the cells; whereby an increase in viability as compared to a control indicates that the modified gene contributes to the resistance of the diploid fungus to the antifungal agent.

28. A method for identifying an antifungal agent that inhibits the growth of a diploid fungus comprising the steps of:

30 (a) providing diploid fungal cells of claim 12; and

(b) culturing the diploid fungal cells under conditions wherein the second allele of the gene is underexpressed and in the presence of a test compound; whereby a loss or reduction of growth of the diploid fungal cells as compared to a control indicates that the test compound is an antifungal agent.

35

29. A method for identifying a therapeutic agent for treatment of a mammalian disease, the method comprising the steps of:

(a) providing diploid cells of claim 10, wherein the modified gene in the diploid cells is an essential gene and displays sequence homology to a mammalian gene associated with the disease;

(b) culturing diploid fungal cells under conditions wherein the second allele of the gene is overexpressed or underexpressed and in the presence of a test compound;

whereby a difference in growth of the diploid fungal cells as compared to a control indicates that the test compound is a therapeutic agent.

30. A method for correlating changes in the levels of proteins with the inhibition of growth or proliferation of a diploid fungal cell, the method comprising the steps of:

(a) generating a first protein expression profile for a control diploid fungal cell which comprises two wild type alleles of the gene;

(b) culturing diploid fungal cells of claim 12 under conditions wherein the second allele of the gene is substantially underexpressed, not expressed or overexpressed, and generating a second protein expression profile for the cultured cells; and

(c) comparing the first protein expression profile with the second protein expression profile to identify changes in the levels of proteins.

31. A method for correlating changes in the levels of gene transcripts with the inhibition of growth or proliferation of a diploid fungal cell, the method comprising the steps of:

(a) generating a transcription profile for a control diploid fungal cell which comprises two wild type alleles of the gene;

(b) culturing diploid fungal cells of claim 12 under conditions wherein the second allele of the gene is substantially underexpressed, not expressed or overexpressed and generating a second transcription profile for the cultured cells; and

(c) comparing the first transcription profile with the second transcription profile to identify changes in the levels of gene transcripts.

32. A purified or isolated nucleic acid molecule consisting essentially of

a nucleotide sequence encoding a gene product required for proliferation of *Candida albicans*, wherein said gene product comprises an amino acid sequence of one of SEQ ID NO:63 to 123.

5 33. The nucleic acid molecule of claim 32, wherein said nucleotide sequence is one of SEQ ID NO:1 to 61.

 34. A nucleic acid molecule comprising a fragment of one of SEQ ID NO.:1 to 62, said fragment selected from the group consisting of fragments comprising at
10 least 10, at least 20, at least 25, at least 30, at least 50 and at least 100 consecutive nucleotides of one of SEQ ID NO: 1 to 62.

 35. A nucleic acid molecule comprising a nucleotide sequence that hybridizes under stringent condition to a second nucleic acid molecule consisting of (a) a
15 nucleotide sequence selected from the group consisting of one of SEQ ID NO.: 1 to 62, or (b) a nucleotide sequence that encodes a polypeptide consisting of an amino acid sequence selected from the group consisting of one of SEQ ID NO.: 63 to 123;
 wherein said stringent condition comprises hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in
20 0.2xSSC/0.1% SDS at about 50-65°C.

 36. The nucleic acid molecule of claim 34 or 35, which consists of the nucleotide sequence selected from the group consisting of one of SEQ ID NO.: 429 to 486.

25 37. A purified or isolated nucleic acid molecule obtained from an organism other than *Candida albicans* or *Saccharomyces cerevisiae* comprising a nucleotide sequence having at least 30% identity to a sequence selected from the group consisting of SEQ ID NO:1-62, fragments comprising at least 25 consecutive nucleotides of
30 SEQ ID NO:1-62, the sequences complementary to SEQ ID NO:1-62 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NO:1-62, as determined using BLASTN version 2.0 with the default parameters.

 38. The purified or isolated nucleic acid molecule of Claim 37, wherein
35 said organism is selected from the group consisting of *Absidia corymbigera*, *Aspergillus flavis*, *Aspergillus fumigatus*, *Aspergillus niger*, *Botrytis cinerea*, *Candida albicans*,

Candida dublinensis, *Candida glabrata*, *Candida krusei*, *Candida parapsilopsis*, *Candida tropicalis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Erysiphe graminis*, *Exophiala dermatiditis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Magnaporthe grisea*, *Mucor rouxii*, *Pneumocystis carinii*, *Puccinia graminis*, *Puccinia recodita*, *Puccinia striiformis*,
5 *Rhizomucor pusillus*, *Rhizopus arrhizus*, *Septoria avenae*, *Septoria nodorum*, *Septoria triticii*, *Tilletia controversa*, *Tilletia tritici*, *Trichosporon beigelii*, and *Ustilago maydis*.

39. A vector comprising a promoter operably linked to the nucleic acid molecule of claim 32, 33, 34, 35, or 37.

10

40. The vector of Claim 39, wherein said promoter is regulatable.

41. The vector of Claim 39, wherein said promoter is active in an organism selected from the group consisting of *Absidia corymbigera*, *Aspergillus flavis*,
15 *Aspergillus fumigatus*, *Aspergillus niger*, *Botrytis cinerea*, *Candida albicans*, *Candida dublinensis*, *Candida glabrata*, *Candida krusei*, *Candida parapsilopsis*, *Candida tropicalis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Erysiphe graminis*, *Exophiala dermatiditis*, *Fusarium oxysporum*, *Histoplasma capsulatum*, *Magnaporthe grisea*, *Mucor rouxii*, *Pneumocystis carinii*, *Puccinia graminis*, *Puccinia recodita*, *Puccinia striiformis*,
20 *Rhizomucor pusillus*, *Rhizopus arrhizus*, *Septoria avenae*, *Septoria nodorum*, *Septoria triticii*, *Tilletia controversa*, *Tilletia tritici*, *Trichosporon beigelii*, and *Ustilago maydis*.

42. A host cell containing the vector of claim 39.

25

43. A purified or isolated polypeptide comprising an amino acid sequence selected from the group consisting of one of SEQ ID NO: 63 to 123.

44. A purified or isolated polypeptide obtained from an organism other than *Candida albicans* or *Saccharomyces cerevisiae* comprising an amino acid sequence
30 having at least 30% similarity to an amino acid sequence selected from the group consisting of one of SEQ ID NO:63 to 123 as determined using FASTA version 3.0t78 with the default parameters.

45. The polypeptide of Claim 44, wherein said organism is selected from the group consisting of *Absidia corymbigera*, *Aspergillus flavis*, *Aspergillus fumigatus*,
35

Aspergillus niger, Botrytis cinerea, Candida albicans, Candida dublinensis, Candida glabrata, Candida krusei, Candida parapsilopsis, Candida tropicalis, Coccidioides immitis, Cryptococcus neoformans, Erysiphe graminis, Exophiala dermatitidis, Fusarium oxysporum, Histoplasma capsulatum, Magnaporthe grisea, Mucor rouxii, Pneumocystis carinii, Puccinia graminis, Puccinia recodita, Puccinia striiformis, Rhizomucor pusillus, Rhizopus arrhizus, Septoria avenae, Septoria nodorum, Septoria triticii, Tilletia controversa, Tilletia tritici, Trichosporon beigelii, and Ustilago maydis.

46. A fusion protein comprising a fragment of a first polypeptide fused to a second polypeptide, said fragment consisting of at least 6 consecutive residues of an amino acid sequence selected from one of SEQ ID NO: 63 to 123.

47. A method of producing a polypeptide, said method comprises introducing into a cell, a vector comprising a promoter operably linked to a nucleotide sequence encoding a polypeptide consisting of an amino acid sequence selected from the group consisting of one of SEQ ID NO:62 to 123; and culturing the cell such that the nucleotide sequence is expressed.

48. A method of producing a polypeptide, said method comprising providing a cell which comprises a heterologous promoter operably linked to a nucleotide sequence encoding a polypeptide consisting of an amino acid sequence selected from the group consisting of one of SEQ ID NO:62 to 123; and culturing the cell such that the nucleotide sequence is expressed.

49. A method for identifying a compound which modulates the activity of a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of one of SEQ ID NO:1 to 62, said method comprising:

- (a) contacting said gene product with a compound; and
- (b) determining whether said compound modulates the activity of said gene product.

50. The method of claim 49, wherein the activity of the gene product is inhibited.

51. The method of Claim 49, wherein said gene product is a polypeptide

and said activity is selected from the group consisting of an enzymatic activity, carbon compound catabolism activity, a biosynthetic activity, a transporter activity, a transcriptional activity, a translational activity, a signal transduction activity, a DNA replication activity, and a cell division activity.

5

52. A method of eliciting an immune response in an animal, comprising introducing into the animal a composition comprising an isolated polypeptide, the amino acid sequence of which comprises at least 6 consecutive residues of one of SEQ ID NO: 63 to 123.

10

53. A strain of *Candida albicans* wherein a first allele of a gene comprising a nucleotide sequence selected from the group consisting of one of SEQ ID NO:1 to 62 is inactive and a second allele of the gene is under the control of a heterologous promoter.

15

54. A strain of *Candida albicans* comprising a nucleic acid molecule comprising a nucleotide sequence selected from one of SEQ ID NO: 1 to 62 under the control of a heterologous promoter.

20

55. The strain of claim 53 or 54, wherein said heterologous promoter is regulatable.

25

56. A method of identifying a compound or binding partner that binds to a polypeptide comprising an amino acid sequence selected from the group consisting of one of SEQ ID NO: 63 to 123 or a fragment thereof said method comprising:

(a) contacting the polypeptide or fragment thereof with a plurality of compounds or a preparation comprising one or more binding partners; and

(b) identifying a compound or binding partner that binds to the polypeptide or fragment thereof.

30

57. A method for identifying a compound having the ability to inhibit growth or proliferation of *Candida albicans*, said method comprising the steps of:

(a) reducing the level or activity of a gene product encoded by a nucleic acid selected from the group consisting of SEQ ID NO: 1 to 62 in a *Candida albicans* cell relative to a wild type cell, wherein said reduced level is not lethal to said cell;

35

- (b) contacting said cell with a compound; and
- (c) determining whether said compound inhibits the growth or proliferation of said cell.

5 58. The method of Claim 57, wherein said step of reducing the level or activity of said gene product comprises transcribing a nucleotide sequence encoding said gene product from a regulatable promoter under conditions in which said gene product is expressed at said reduced level.

10 59. The method of claim 58, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of polypeptides encoded by SEQ ID NO: 63 to 123.

15 60. A method for inhibiting growth or proliferation of *Candida albicans* cells comprising contacting the cells with a compound that (i) reduce the level of or inhibit the activity of a nucleotide sequence selected from the group consisting of SEQ ID NO:1 to 62, or (ii) reduce the level of or inhibit the activity of a gene product encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:1 to 62.

20 61. The method of claim 60, wherein said gene product is a polypeptide comprising an amino acid sequence selected from the group consisting of polypeptides encoded by SEQ ID NO: 63 to 123.

25 62. The method of claim 60, wherein the compound is an antibody, a fragment of an antibody, an antisense nucleic acid molecule, or a ribozyme.

 63. A method for manufacturing an antimycotic compound comprising the steps of:

- 30 (a) screening a pluralities of candidate compounds to identify a compound that reduces the activity or level of a gene product encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 to 61; and
- (b) manufacturing the compound so identified.

35 64. The method of claim 63, wherein said gene product is a polypeptide comprising an amino acid sequence selected from the group consisting of polypeptides

encoded by SEQ ID NO: 1 to 61.

65. A method for treating an infection of a subject by *Candida albicans* comprising administering a pharmaceutical composition comprising a therapeutically effective amount of a compound that reduces the activity or level of a gene product encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1 to 62 and a pharmaceutically acceptable carrier, to said subject.

66. The method of claim 65, wherein the compound is an antibody, a fragment of an antibody, an antisense nucleic acid molecule, or a ribozyme.

67. A method for preventing or containing contamination of an object by *Candida albicans* comprising contacting the object with a composition comprising an effective amount of a compound that reduces the activity or level of a gene product encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1 to 62.

68. A method for preventing or inhibiting formation on a surface of a biofilm comprising *Candida albicans*, said method comprising contacting the surface with a composition comprising an effective amount of a compound that reduces the activity or level of a gene product encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1 to 62.

69. A pharmaceutical composition comprising a therapeutically effective amount of an agent which reduces the activity or level of a gene product encoded by a nucleic acid selected from the group consisting of SEQ ID NO: 1 to 61 in a pharmaceutically acceptable carrier.

70. The method of claim 65, wherein said subject is selected from the group consisting of a plant, a vertebrate, a mammal, an avian, and a human.

71. An antibody preparation which binds the polypeptide of claim 43 or 44.

35

72. The antibody preparation of claim 71 which comprises a monoclonal antibody.

5 73. A method for evaluating a compound against a target gene product encoded by a nucleotide sequence comprising one of SEQ ID NO: 1 to 61, said method comprising the steps of:

(a) contacting wild type diploid fungal cells with the compound and generating a first protein expression profile;

10 (b) determining the protein expression profile of diploid fungal cells of claim 12 which have been cultured under conditions wherein the second allele of the target gene is substantially underexpressed, not expressed or overexpressed and generating a second protein expression profile for the cultured cells; and

(c) comparing the first protein expression profile with the second
15 protein expression profile to identify similarities in the profiles.

74. A method for evaluating a compound against a target gene product encoded by a nucleotide sequence comprising one of SEQ ID NO: 1 to 61, said method comprising the steps of:

20 (a) contacting wild type diploid fungal cells with the compound and generating a first transcription profile;

(b) determining the transcription profile of diploid fungal cells of claim 12 which have been cultured under conditions wherein the second allele of the target gene is substantially underexpressed, not expressed or overexpressed and generating a
25 second transcription profile for the cultured cells; and

(c) comparing the first transcription profile with the second transcription profile to identify similarities in the profiles.

30 75. A method for identifying an antimycotic compound comprising screening a plurality of compounds to identify a compound that reduces the activity or level of a gene product, said gene product being encoded by a nucleotide sequence that is naturally occurring in *Saccharomyces cerevisiae* and that is the ortholog of a gene having a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 to 61.

35

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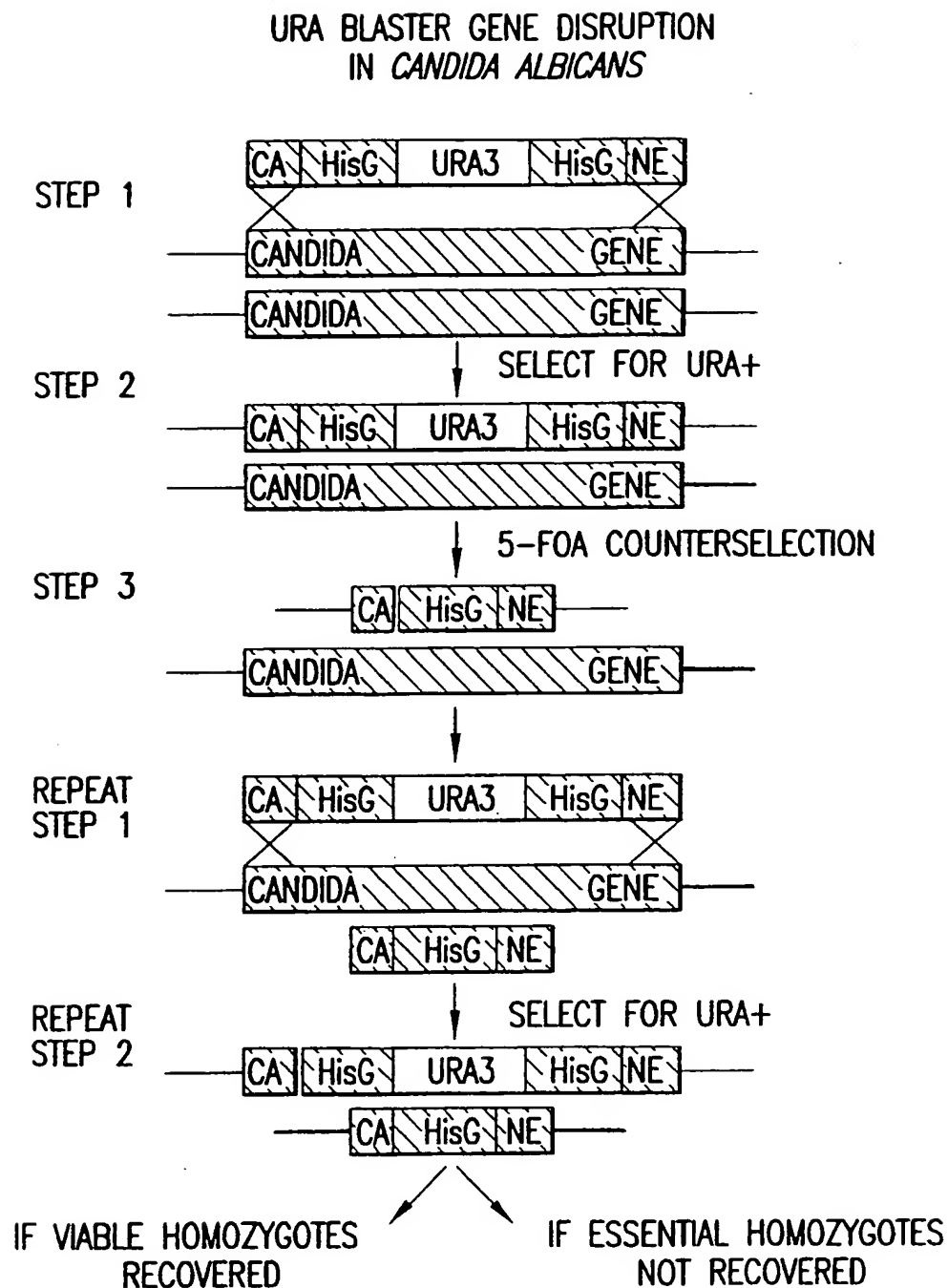
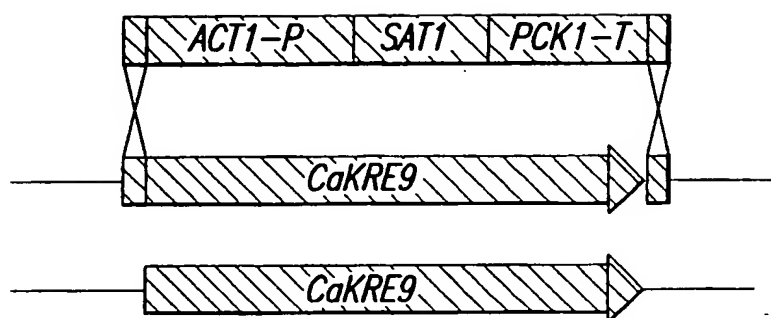


FIG.1

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- STEP 1: GENE REPLACEMENT



- STEP 2: CONDITIONAL EXPRESSION
BY PROMOTER REPLACEMENT

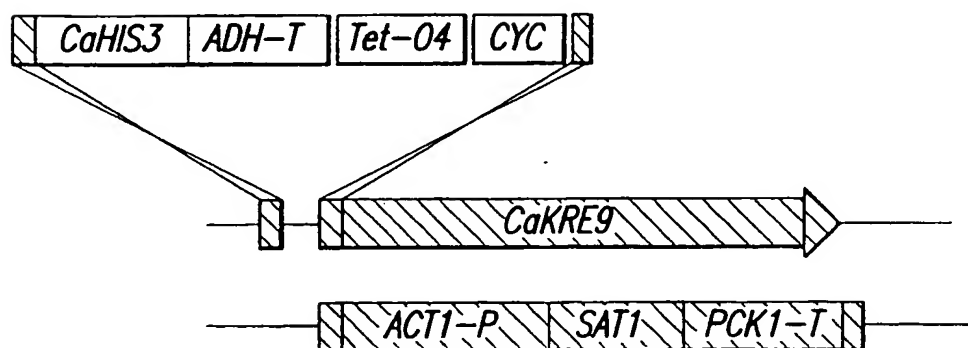


FIG. 2A

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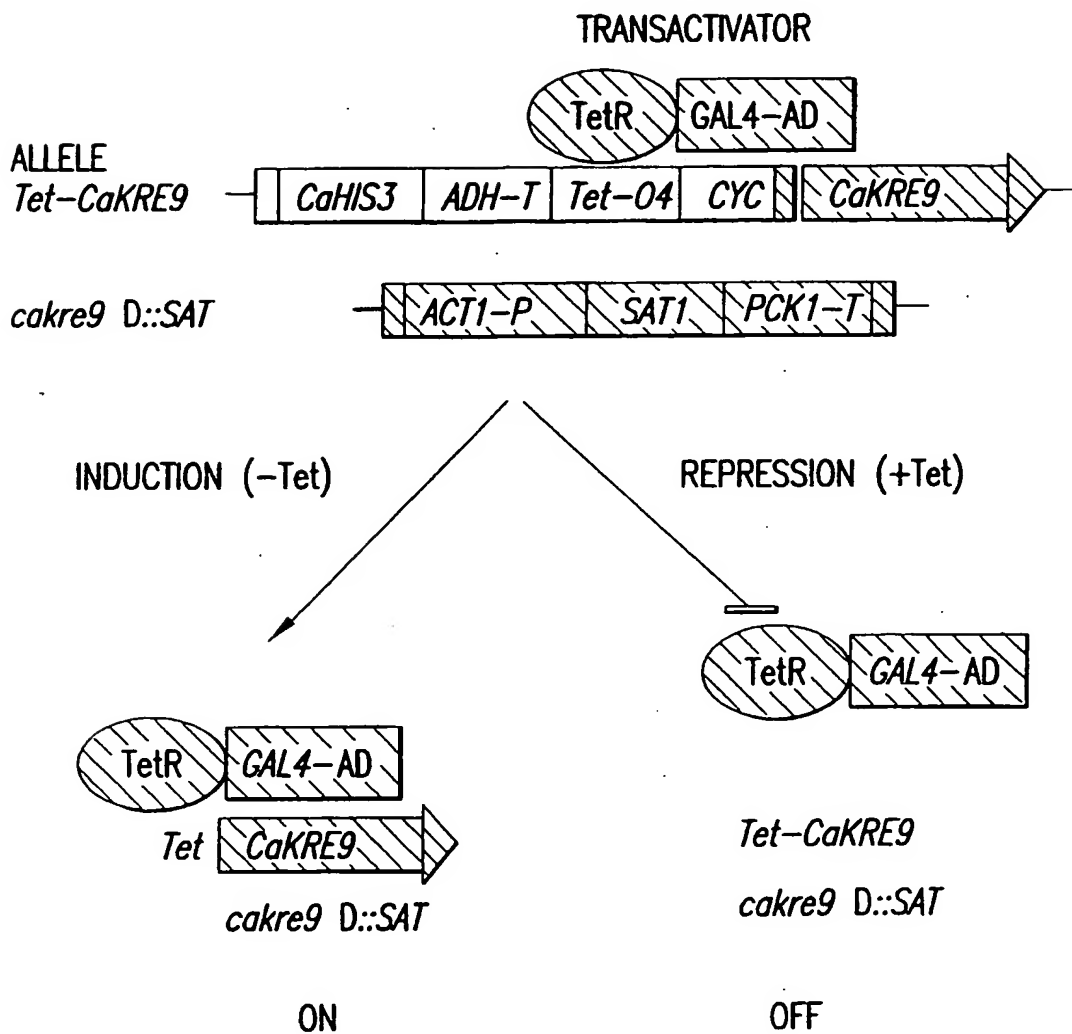
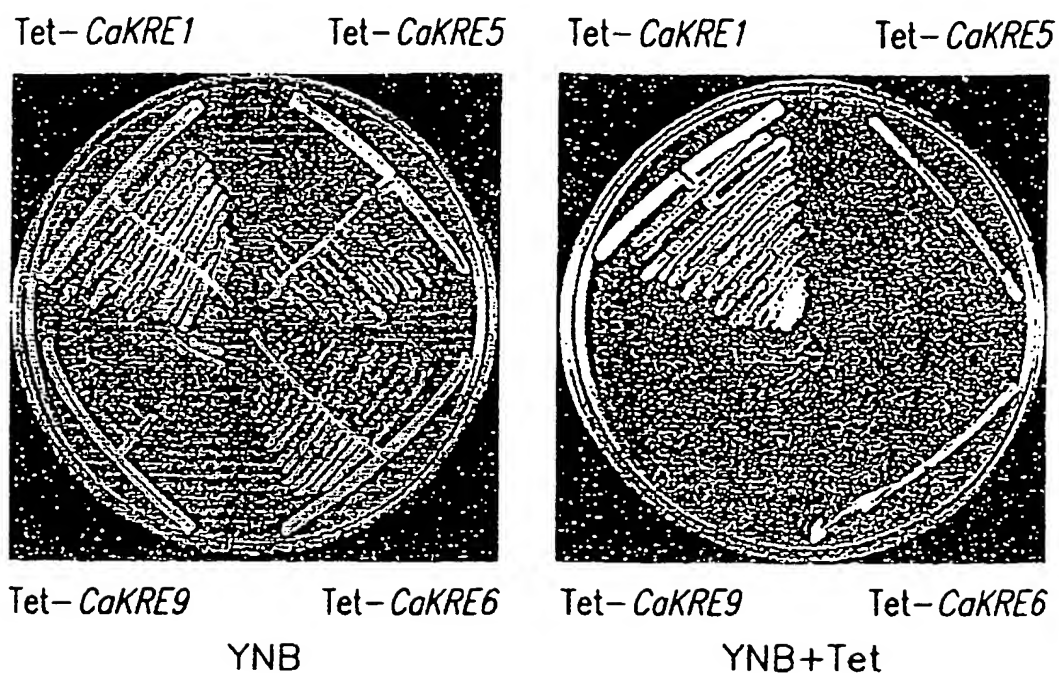
C. ALBICANS GRACE CONDITIONAL EXPRESSION

FIG. 2B

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GRACE Validation of *CaKRE* Targets

GENE	<i>S. cerevisiae</i>	<i>C. albicans</i> URA blaster	<i>C. albicans</i> GRACE
<i>KRE1</i>	Viable	Viable	Viable
<i>KRE5</i>	Essential	Essential	Essential
<i>KRE6</i>	Essential + <i>skn1Δ</i>	Essential	Essential
<i>KRE9</i>	Essential + <i>knh1Δ</i>	Essential	Essential

FIG.3

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Target Validation by GRACE Method

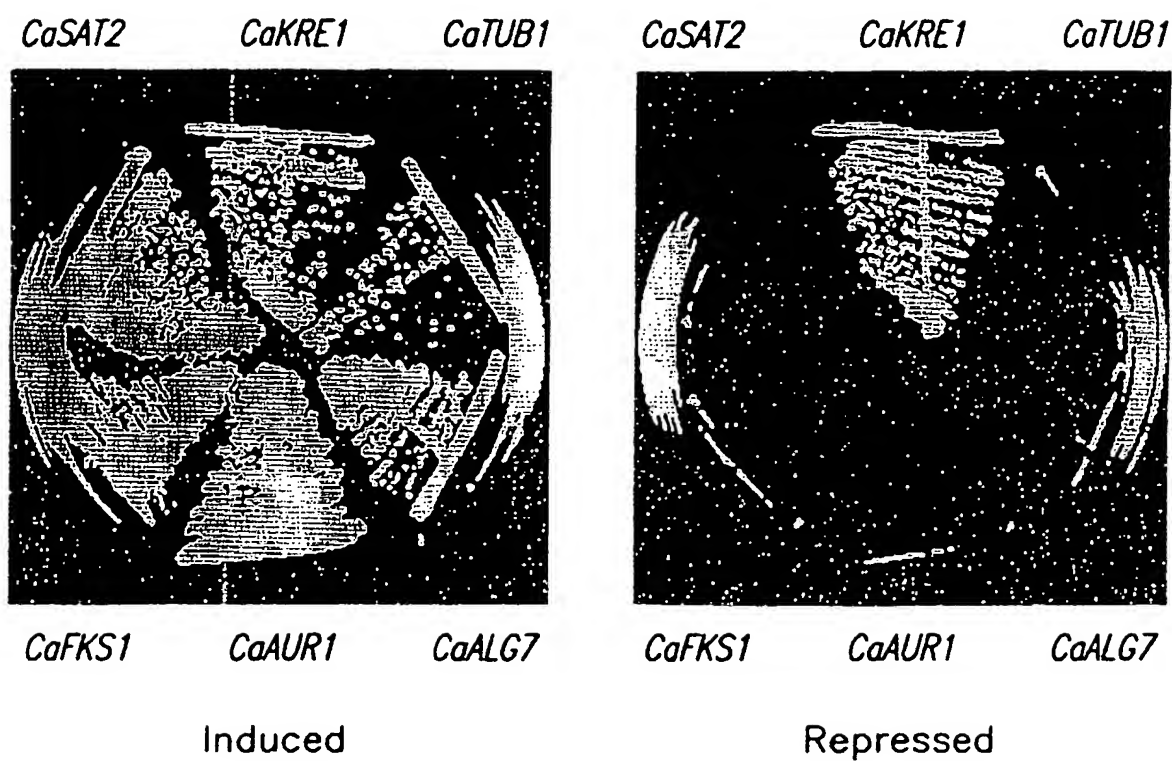


FIG.4

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Constitutive Expression Levels of
GRACE Strains

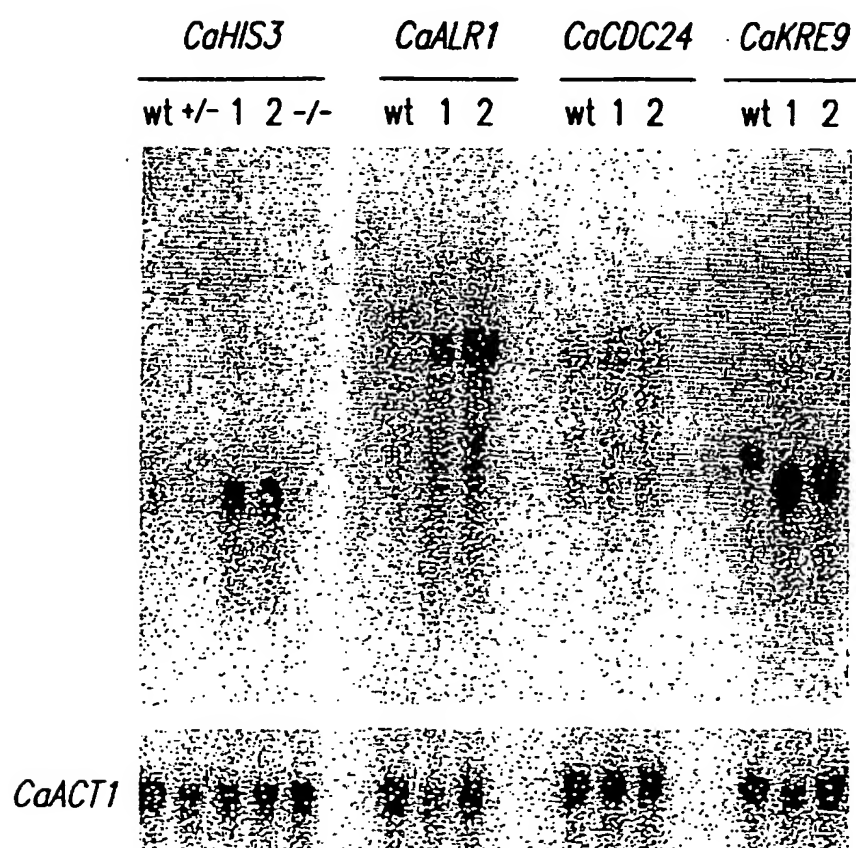


FIG.5

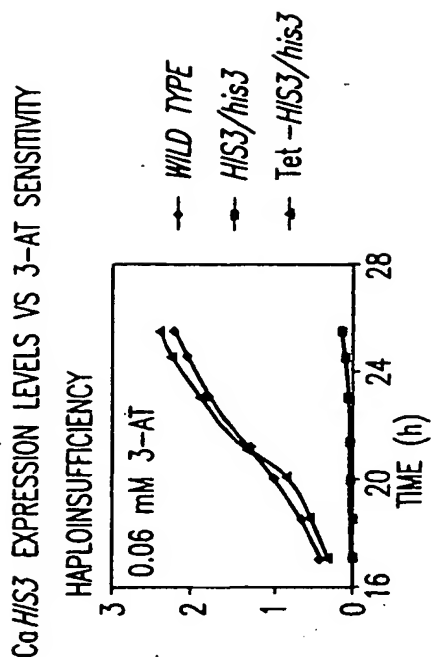


FIG. 6B

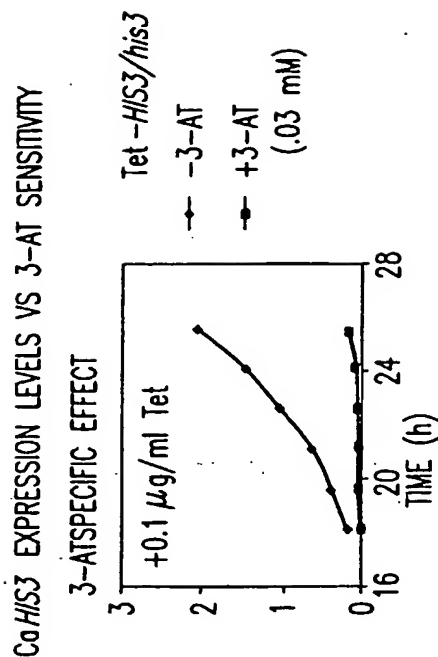


FIG. 6D

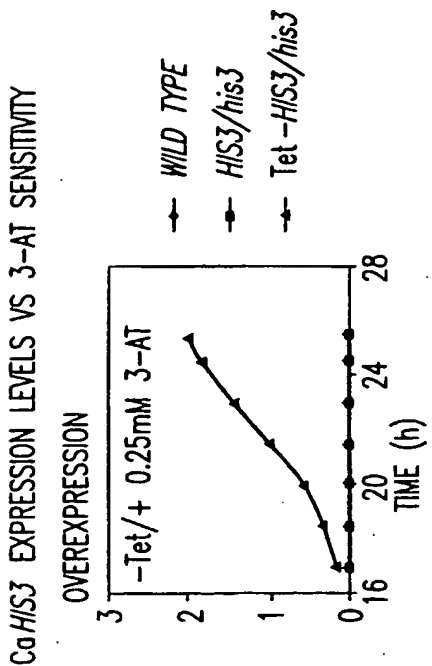


FIG. 6A

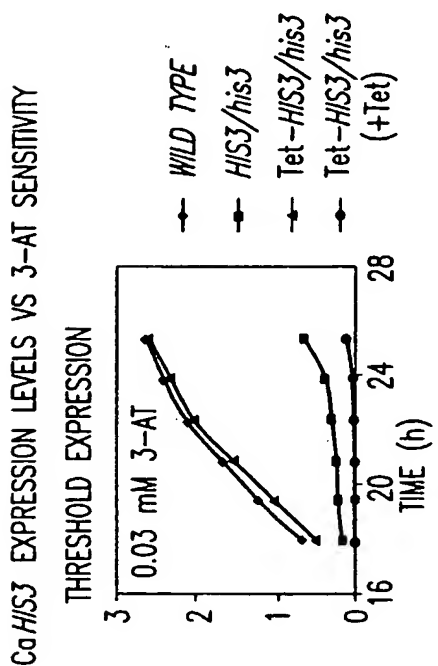


FIG. 6C

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<211> 1695

<212> DNA

<213> Candida albicans

<400> 6

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<211> 1521

<212> DNA

<213> Candida albicans

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<211> 1599

<212> DNA

<213> Candida albicans

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<212> DNA
<213> Candida albicans

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<210> 11
<211> 999
<212> DNA
<213> Candida albicans

<400> 11
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<212> DNA

<213> Candida albicans

<400> 12

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<212> DNA

<213> Candida albicans

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<211> 2280

<212> DNA

<213> Candida albicans

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<211> 1587

<212> DNA

<213> Candida albicans

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<213> Candida albicans

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<213> Candida albicans

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<211> 1092

<212> DNA

<213> *Candida albicans*

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<212> DNA

<213> *Candida albicans*

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<211> 1911

<212> DNA

<213> Candida albicans

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<210> 21

<211> 984

<212> DNA

<213> *Candida albicans*

<400> 21

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<210> 22

<211> 1659

<212> DNA

<213> *Candida albicans*

<400> 22

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<210> 23

<211> 2148

<212> DNA

<213> *Candida albicans*

<400> 23

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<210> 24

<211> 3363

<212> DNA

<213> *Candida albicans*

<400> 24

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<210> 25

<211> 591

<212> DNA

<213> Candida albicans

<400> 25

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<210> 26

<211> 1416

<212> DNA

<213> Candida albicans

<400> 26

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<210> 27

<211> 3540

<212> DNA

<213> Candida albicans

<400> 27

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<210> 28

<211> 837

<212> DNA

<213> Candida albicans

<400> 28

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<210> 29

<211> 1479

<212> DNA

<213> Candida albicans

<400> 29

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<210> 30

<211> 1230

<212> DNA

<213> Candida albicans

<400> 30

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ggtggcacta	caacgacgac	aacaggaaca	gtgaatatca	atcttaatca	acaaataata	180
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aaattaactt	attttagtag	tgatgatgaa	aatagttctg	atggatcagt	tttggagaat	720
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<210> 31

<211> 984

<212> DNA

<213> Candida albicans

<400> 31

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agaatgatt	catcattaat	ggtattttca	tcaaataata	aaaaaagacc	aaagacttta	300
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<210> 32

<211> 378

<212> DNA

<213> Candida albicans

<400> 32

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gacaaattag	agacgatgaa	tggaggaact	gccagtgtag	cattaatttt	agcaaactgg	180
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aataacaaag	aggctttccc	tgaaccatta	gtaagagtgc	gtgttggaca	atcaaataaa	300
gaaaatcaag	acgatgaaga	agcagatgaa	gaagaagggtg	ttagagatat	tgaagaagtt	360
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<210> 33

<211> 3363

<212> DNA

<213> Candida albicans

<400> 33

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<213> *Candida albicans*

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<211> 1740

<212> DNA

<213> *Candida albicans*

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<210> 36

<211> 5694

<212> DNA

<213> Candida albicans

<400> 36

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<211> 1203

<212> DNA

<213> Candida albicans

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<210> 38

<211> 837

<212> DNA

<213> Candida albicans

<400> 38

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<210> 39

<211> 1347
 <212> DNA
 <213> *Candida albicans*

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<210> 40
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 <212> DNA
 <213> *Candida albicans*

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attgataatt	tatttagaac	gttcaagact	attagtaaa	ttcaattgtt	acacaacggt	660
agctttttga	tttcagtttt	gggggttgaa	ttgaattttg	tcaagtacta	tttgggtcaa	720
tcaattttca	ccactttggt	ttacggattt	attttgagca	ttccatgtgt	ttactttgga	780
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<210> 41
 <211> 582
 <212> DNA
 <213> *Candida albicans*

<400> 41

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tgtttgata	atgggtaaatc	tgaatataaaa	aggtttcata	acggagaaac	attagaagtt	420
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ggtaaaaaaga	agcaaccaat	gtggttgaca	ctgagaaatg	ccacaatgtt	gccacagga	540
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<210> 42

<211> 1299

<212> DNA

<213> Candida albicans

<400> 42

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<210> 43

<211> 2307

<212> DNA

<213> Candida albicans

<400> 43

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<210> 44

<211> 3129

<212> DNA

<213> Candida albicans

<400> 44

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gatgatgatt	ataatgctga	gaaatatttc	gatgatggtg	atgacgatga	tgagggtgat	840
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<210> 47

<211> 1524

<212> DNA

<213> Candida albicans

<400> 47

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gaatatggac	ctaccgttct	tcccattcta	ttaactcttg	ctggagccaa	gtattatttc	240
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<210> 48

<211> 993

<212> DNA

<213> Candida albicans

<400> 48

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<210> 49

<211> 666

<212> DNA

<213> *Candida albicans*

<400> 49

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<210> 50

<211> 2367

<212> DNA

<213> *Candida albicans*

<400> 50

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caaacactg	atattgtaag	agttcatgat	gttaaagaaa	tgaaagatgt	agtatgtata	2340
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<210> 51

<211> 447

<212> DNA

<213> Candida albicans

<400> 51

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tatcaaaactg	gatttcaacg	atttttaatc	attggttata	ttcaagaatt	aatgaaattt	180
tggttatccc	atatagatca	atataataac	tcttcttcac	ttcggaatca	tttgaataat	240
ttggaaaata	ttttggcaca	aatttctata	acgaatggag	ataaagaagt	tgaagattat	300
gaaaaaaata	ttaaaaaggc	aagaaataaa	ttaagagtga	tagctagtat	aactaaagaa	360
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<210> 52

<211> 810

<212> DNA

<213> Candida albicans

<400> 52

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gcatcatctt	acattaataa	agggtttact	cgaactatcc	aagcagaaaa	caaaccatg	180
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cgatcagtg	tggttatgga	accgatcagt	gatgttagta	atcaatataa	tatgaattat	480
gaatcgaaaa	aattgaccgg	aggattgaat	gatattgaag	ctgggaaatt	ggaaaagcaa	540
aatgaagggt	aagatgggga	tggggatgaa	ctggaagtta	aaaagaagaa	aagaaaagga	600
cctaaagaac	caaaccatt	aagtgtcaaa	aagaagaaaa	cagataatgc	aactgctgcc	660
agtactaatc	aagagcagaa	aaagaaacca	aatagaagaa	aaagacatgg	caagtcaaaa	720
gcagaagaga	aggaagacca	agaacaggag	caagtgaacg	aagcaacaac	taatgaagat	780
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<210> 53

<211> 921

<212> DNA

<213> Candida albicans

<400> 53

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accgcctttt	tccatgtctt	gaccaacttg	aaccagttca	tcaacgaaac	caaatacaagt	180
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aaaagagggtg	ctaataatggt	ggtcatgcta	tgtatagtac	taggtgtggt	attagtgttg	900
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<210> 54

<211> 579

<212> DNA

<213> Candida albicans

<400> 54

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tctacagaag	ataagactac	tcataaagat	gaaaccaaac	caataatagt	tttgaagcaa	180
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ggtgtaaaca	cgtttgaaaa	agtggagact	acaaaacaat	caatgatcaa	aaagatcgaa	300
tcagaagatt	ccgatgatga	ctccagcgat	gatagaaaaa	tccaataga	tgaatttgggt	360
gcagcatttt	taagaggact	tggttggcaa	gaagaagagg	aaaagaacaa	ggatgacagc	420
aaatccacta	acactcaaaa	tttatctcat	aggaaacatg	gaatcacctt	agggattgga	480
gcaaaaccta	tagatgaaga	aataatacaa	gattttaaact	ctacggaaaa	aggtattcca	540
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<210> 55

<211> 2145

<212> DNA

<213> Candida albicans

<400> 55

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agttcatcat	ctggggaaag	caatgcccc	aaacgtgctg	atggaaaaagc	caaggaagtc	180
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gaagaggaag	atgaagaagc	aatgaaggaa	aacttgaaaa	aattagaggc	agacgatcca	360
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aataaagcag	aggtacaaca	atttttgagt	gactttgaat	gggaaaagac	acctttgggt	1980
caatatgtta	gtgtacaaaag	acagttgaaa	gcagaaagat	taagaatctt	gaaagaagcc	2040
caagaagagg	aagcaaaagc	acaagctgaa	caaaagaaaa	aagaagaaga	agaggatgag	2100
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<210> 56

<211> 846

<212> DNA

<213> Candida albicans

<400> 56

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<210> 57

<211> 2550

<212> DNA

<213> Candida albicans

<400> 57

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caattgaaag	aacaacagga	atctacaacc	aagatgctgt	tgtctgaaag	agatttggtta	300
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<210> 58

<211> 3294

<212> DNA

<213> Candida albicans

<220>

<221> misc_feature

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<223> n = A,T,C or G

<400> 58

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gcccatact	ctcttaaagt	tgaaaaattg	gagattctta	gtttcaataa	cggtgaaact	3180
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<210> 59

<211> 1563

<212> DNA

<213> Candida albicans

<400> 59

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<210> 60

<211> 597

<212> DNA

<213> Candida albicans

<400> 60

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<210> 61

<211> 2127

<212> DNA

<213> Candida albicans

<400> 61

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<210> 62

<211> 3293

<212> DNA

<213> Candida albicans

<400> 62

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<210> 63

<211> 219

<212> PRT

<213> Candida albicans

<400> 63

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Arg Leu Pro Thr Ser Val Lys Lys Lys Lys Lys Leu Ile Gln Glu Cys
          35           40           45
Gln Leu Ser Ile Leu Leu Gly Ser Gly Gly His Thr Gly Glu Met Met
          50           55           60
Arg Ile Ile Ser Lys Leu Asp Met Gly Lys Val Ser Arg Thr Trp Ile
65           70           75           80
Tyr Thr Ser Gly Asp Asn Ala Ser Leu Ala Lys Ala Gln Asp Tyr Glu
          85           90           95
Arg Lys Ser Gly Thr Ser Ser Gln Tyr Ile Pro Ile Pro Arg Ala Arg
          100          105          110
Thr Val Gly Gln Ser Tyr Ile Ser Ser Ile Pro Thr Thr Ile Tyr Ser
          115          120          125
Phe Leu Phe Ser Ala Ile Ala Met Leu Lys His Arg Pro Ala Val Ile
          130          135          140
Leu Leu Asn Gly Pro Gly Thr Cys Val Pro Val Ala Tyr Ile Leu Phe
145          150          155          160
Leu Tyr Lys Leu Leu Gly Leu Cys Asn Thr Lys Ile Ile Tyr Ile Glu
          165          170          175
Ser Leu Ala Arg Val Asn Lys Leu Ser Leu Ser Gly Leu Leu Leu
          180          185          190
Pro Ile Ser Asp Arg Phe Ile Val Gln Trp Glu Ser Leu Tyr Gln Gln
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Tyr Ser Arg Val Glu Tyr Tyr Gly Ile Leu Ile
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<210> 64
 <211> 167
 <212> PRT
 <213> Candida albicans

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 35 40 45
 Ile Ser Ala Ile Lys Gln Ile Thr Lys Lys Leu Asn Lys Phe Ser Lys
 50 55 60
 Ser Lys Asn Ser His Thr Ile Asn Lys Phe Gln Asn Glu Gln Tyr Lys
 65 70 75 80
 Thr Ile Lys Tyr Ile Ala Val Lys Gly Met Gly Lys Thr Ile Glu Lys
 85 90 95
 Val Ala Ser Ile Gly Thr His Phe Gln Lys Asp Tyr Lys Val Asp Val
 100 105 110
 Leu Thr Gly Ser Thr Thr Val Leu Asp Glu Phe Ala Pro Ile Glu Ser
 115 120 125
 Asn Gln Glu Pro Asp Asn Glu Asn Lys Ser Asp Asp Asp Asp Asp
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 Arg Ile Trp Ile Lys Arg Asp
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<210> 65
 <211> 494
 <212> PRT
 <213> Candida albicans

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 Ile Gly Tyr Val Ala Thr Leu Ser Val Ile Pro Lys Val Ser Pro Ser
 35 40 45
 Phe Val Lys Ile Gly Leu Lys Gly Lys Asp Leu Ser Lys Pro Pro Pro
 50 55 60
 Val Ser Glu Ile Pro Glu Thr Met Gly Leu Val Ala Ser Thr Thr Tyr
 65 70 75 80
 Met Phe Leu Met Phe Gly Leu Ile Pro Phe Ile Phe Phe Lys Tyr Leu
 85 90 95
 Val Ser Phe Gly Ser Met Ser Asn Asp Glu Val Ile Thr Lys Asn Tyr
 100 105 110
 Leu Ser Gln Tyr Gln Ser Leu Ala Asp Asn Arg Leu Phe Pro His Asn
 115 120 125
 Lys Leu Ala Glu Tyr Leu Ser Ala Leu Leu Cys Leu Gln Ser Thr Thr
 130 135 140
 Leu Leu Gly Leu Leu Asp Asp Leu Phe Asp Ile Arg Trp Arg His Lys
 145 150 155 160
 Phe Phe Leu Pro Ala Val Ala Ser Leu Pro Leu Leu Ile Val Tyr Tyr
 165 170 175

Val Asp Phe Ser Val Thr Ser Val Val Ile Pro Lys Phe Val Thr Glu
 180 185 190
 Phe Pro Gly Gly Tyr Val Leu Ile Asn Thr Ile Asn Phe Phe Ile Lys
 195 200 205
 Tyr Ser Asn His Leu Val Thr Ser Ile Thr Gly Leu Ser Phe Arg Thr
 210 215 220
 Leu Gln Thr Asp Tyr Val Val Pro Asp Ser Ser Pro Lys Leu Ile Asp
 225 230 235 240
 Leu Gly Ile Phe Tyr Tyr Val Tyr Met Ser Ala Ile Ser Ile Phe Ser
 245 250 255
 Pro Asn Ser Ile Asn Ile Leu Ala Gly Val Asn Gly Leu Glu Val Gly
 260 265 270
 Gln Ser Leu Val Leu Ala Ala Ile Phe Leu Ile Asn Asp Phe Cys Tyr
 275 280 285
 Leu Phe Ser Pro Gly Ile Ser Gln Ala Ala His Asp Ser His Met Phe
 290 295 300
 Ser Val Val Phe Ile Ile Pro Phe Val Gly Val Ser Leu Ala Leu Leu
 305 310 315 320
 Gln Tyr Asn Trp Phe Pro Ala Arg Val Phe Val Gly Asp Thr Tyr Cys
 325 330 335
 Tyr Phe Ser Gly Met Val Phe Ala Ile Val Gly Ile Ile Gly His Phe
 340 345 350
 Ser Lys Thr Leu Leu Ile Phe Leu Leu Pro Gln Ile Ile Asn Phe Val
 355 360 365
 Tyr Ser Val Pro Gln Leu Phe His Ile Leu Pro Cys Pro Arg His Arg
 370 375 380
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 385 390 395 400
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 405 410 415
 Ser Phe Phe Lys Leu Ile Lys Val Glu Arg Gly Ser Lys Ser Asn Gln
 420 425 430
 Ile Val Arg Phe Ser Asn Met Thr Ile Ile Asn Leu Thr Leu Val Trp
 435 440 445
 Val Gly Pro Leu Arg Glu Asp Gln Leu Cys Ile Ser Ile Leu Val Val
 450 455 460
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<210> 66

<211> 280

<212> PRT

<213> Candida albicans

<400> 66

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 35 40 45
 Ile Ser Thr Asp Leu Ser Thr Ile Lys Lys Phe Phe Gln Lys Val Ala
 50 55 60
 Ile Gly Ser Thr Ile Glu Ser Phe Ile Asn Ser Leu Leu Thr Asp Tyr
 65 70 75 80

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Pro Glu Asp Ile Trp Ile Asn Leu Thr Lys Leu Thr Ser Asp Leu Asp
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Leu Val Asp Ala Val Asp Glu Gln Ala Ser Lys Leu Pro Lys Asn Cys
      100        105        110
Gly Ile Val Ala Phe Ile Asp Lys Ala Ser Phe Thr Leu Ala Phe Asn
      115        120        125
Ser Leu Lys Lys Leu Ser Ser Ser Leu Thr Glu Cys Glu Trp Pro Ile
      130        135        140
Gln Gln Phe Thr Ser Asn Tyr Tyr Leu Lys Gln Tyr Gln Lys Gln Ile
      145        150        155        160
Leu Asp Pro Asn Ser Leu Thr Glu Glu Val Ser Gln Ala Leu Ile Asp
      165        170        175
Phe Asp Lys Ala Glu Gln Gln Ser Ile Glu Glu Leu Gln Ser Gln Arg
      180        185        190
Asn Leu Val Asp Glu Asp Gly Phe Thr Leu Val Val Gly Ser His Arg
      195        200        205
Lys Thr Lys Ala Gly Ile Leu Gly Lys Gln Lys Leu Ala Ser Thr Val
      210        215        220
Gly Val Val Lys Ala Gln Ser Lys Met Lys Ser Lys Glu Lys Gln Asp
      225        230        235        240
Phe Tyr Arg Phe Gln Leu Arg Gln Arg Lys Lys Glu Glu Met Asn Glu
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Glu Lys Lys Arg Phe Arg Pro Tyr
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<210> 67

<211> 371

<212> PRT

<213> Candida albicans

<400> 67

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      20          25          30
Lys Asp Ala Leu Lys Gly Lys Gly Ser Ser Met Ser Leu His Tyr Ile
      35          40          45
Asp Glu Ile Thr Glu Leu Tyr Lys Arg Val Gln Ser Gln Lys Val Lys
      50          55          60
Asp Thr Arg Val His Leu Glu Asp Ser Glu Val Phe Lys Glu Ala Ser
      65          70          75          80
Asp Phe Ala Ala Leu Asn Ala Arg Asn Ile Val Phe Asp Asp Ser Gly
      85          90          95
Ile Ala Leu Asp Asp Lys Glu Phe Phe Lys Cys Leu Arg Arg Phe Ala
      100        105        110
Val Thr Asp Pro Ser Leu Leu Ser Arg Asn Asp Ile Gly Asp Asn Asp
      115        120        125
Gly Asn Asn Ser Asn Asp Glu Asp Asp Val Asp Asp Asp Ser Asp
      130        135        140
Glu Glu Glu Glu Ala Ile Thr Asp Glu Tyr Thr Phe Asn Lys Thr Asn
      145        150        155        160
Trp Leu Lys Leu Gly Ile Leu Tyr His Gln Val Ser Lys Lys Ser Ile
      165        170        175
Ser Val Asp Phe Leu Asn Gly Pro Leu Lys Ala Glu Lys Arg Lys Ile
      180        185        190

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 Tyr Asp Gly Asn Gly Val Asn Leu Phe Lys Phe Phe Ile Asn Pro Arg
 245 250 255
 Ser Phe Gly Gln Ser Val Glu Asn Leu Phe Tyr Thr Ser Phe Leu Val
 260 265 270
 Lys Asp Gly Arg Leu Lys Leu Tyr Val Asn Asn Asp Gly Met Pro Cys
 275 280 285
 Ile Gln Arg Val Ser Ser Asp Glu Ile Arg Glu Ala Gln Leu Glu Ser
 290 295 300
 Asn Lys Ile Phe Ala Ser His His Ile Ala Ser Phe Asn Tyr Lys Ala
 305 310 315 320
 Trp Lys Lys Tyr Thr Gln Leu Tyr Asn Ile Arg Glu Ala Phe Leu Gly
 325 330 335
 His Arg Asp Glu Pro Glu Asp Gln Met Pro Pro Glu Asp Ile Ile Asp
 340 345 350
 Tyr Asn Asp Glu Glu Pro Ile Pro Ser Ser Gln Arg Arg Asp Ser Asn
 355 360 365
 Ser Ser Asp
 370

<210> 68

<211> 564

<212> PRT

<213> Candida albicans

<400> 68

Met Ala Arg Arg Asn Arg Asn Lys Thr Val Asn Glu Glu Glu Ile Glu
 1 5 10 15
 Leu Asp Glu Val Asp Ser Phe Asn Ala Asn Arg Glu Lys Ile Leu Leu
 20 25 30
 Asp Glu Ala Gly Glu Tyr Gly Arg Asp Asp Gln Ser Glu Glu Asp Asp
 35 40 45
 Ser Glu Glu Glu Val Met Gln Val Glu Glu Asp Ser Glu Asp Asp Glu
 50 55 60
 Glu Asp Gln Glu Asp Glu Glu Glu Glu Glu Glu Glu Gly Glu
 65 70 75 80
 Glu Glu Glu Glu Glu Glu Lys Gly Trp Gly Gly Arg Gln Asn Tyr
 85 90 95
 Tyr Gly Gly Asp Asp Leu Ser Asp Asp Glu Asp Ala Lys Gln Met Thr
 100 105 110
 Glu Glu Ala Leu Arg Gln Gln Lys Lys His Leu Gln Glu Leu Ala Met
 115 120 125
 Asp Asp Tyr Leu Asp Asp Glu Met Met Glu Asp Trp Gln Lys Lys Ala
 130 135 140
 Asp Ser Tyr Asp Asn Lys Asp Thr Ser Ser Ser Thr Gln Gln Gln Gln
 145 150 155 160
 Gln Gln Gln Leu Ile Glu Ser Asn Ser Ser Ile Ala Asn Leu Glu
 165 170 175
 Asp Ser Asp Lys Leu Lys Leu Leu Gln Gln Ser Phe Pro Glu Phe Ile
 180 185 190
 Pro Leu Leu Lys Glu Leu Asn Ser Leu Lys Val Lys Leu Glu Asp Leu
 195 200 205

Gln Lys Leu Glu Asp Lys Asn Lys Cys Ile Glu Thr Lys Ile Val Ala
 210 215 220
 Leu Ser Ala Tyr Leu Gly Ala Ile Ser Ser Tyr Phe Ala Ile Phe Val
 225 230 235 240
 Asp Asn Leu Asn Asn Glu Glu Ser Phe Val Ser Met Lys Asp Asn Pro
 245 250 255
 Ile Met Glu Thr Ile Leu Ser Ser Arg Glu Ile Trp Arg Gln Ala Asn
 260 265 270
 Glu Leu Pro Asp Asp Ile Lys Leu Asp Asp Val Lys Val His Val Ser
 275 280 285
 Asp Val Val Ser Ser Ser Asp Ile Asp Asp Glu Asp Asn Phe Val Asp
 290 295 300
 Ala Lys Glu Glu Gln Ser Glu Asp Glu Glu Ile Ser Glu Glu Glu Val
 305 310 315 320
 Ser Gln Asp Glu Asp Glu Asp Gln Ser Asp Asp Leu Asp Ile Asp Ala
 325 330 335
 Asn Ser Glu Arg Ile Ile Lys His Val Ser Lys Lys His Gly Asp Asp
 340 345 350
 Phe Thr Glu Ala Asp Ile Glu Asp Ile Asp Met Glu Asp Lys Gln Arg
 355 360 365
 Arg Lys Lys Thr Leu Arg Phe Tyr Thr Ser Lys Ile Asp Lys Ala Ala
 370 375 380
 Ala Lys Lys Asp Gln Ser Tyr Ser Gly Asp Ile Asp Val Pro Tyr Lys
 385 390 395 400
 Glu Arg Leu Phe Glu Arg Gln Gln Arg Leu Leu Glu Glu Ala Arg Lys
 405 410 415
 Arg Gly Leu Gln Lys Gln Asp Asp Glu Asn Ile Ser Asp Asn Asp Asn
 420 425 430
 Asp Asn Asp Gly Val Asn Asp Asp Glu Gly Phe Glu Gln Gly Asp Asp
 435 440 445
 Tyr Tyr Glu Ser Ile Lys Gln His Lys Leu Asn Lys Lys Gln Ser Arg
 450 455 460
 Lys Ser Ala His Glu Ala Ala Val Lys Ala Ala Lys Glu Gly Lys Leu
 465 470 475 480
 Ala Glu Leu Gln Glu Ala Val Gly Gln Asp Gly Lys Arg Ala Ile Asn
 485 490 495
 Tyr Gln Ile Leu Lys Asn Lys Gly Leu Thr Pro His Arg Lys Lys Glu
 500 505 510
 Tyr Arg Asn Ser Arg Val Lys Lys Arg Lys Gln Tyr Glu Lys Ala Gln
 515 520 525
 Lys Lys Leu Lys Ser Val Arg Gln Val Tyr Asp Ala Asn Asn Arg Gly
 530 535 540
 Pro Tyr Glu Gly Glu Lys Thr Gly Ile Lys Lys Gly Leu Ser Lys Ser
 545 550 555 560
 Val Lys Leu Val

<210> 69
 <211> 506
 <212> PRT
 <213> Candida albicans

<400> 69
 Met Ser Lys Val Glu Glu His Glu Ser Val Asn Asn Leu Lys Arg Lys
 1 5 10 15
 Phe Pro Ser Leu Ala Lys Pro Arg Gln Pro Leu Lys Glu Thr Asn Ser
 20 25 30

Asn Ile Pro Ser Pro His Lys Arg Ala Lys Ile Glu Ser Pro Ser Lys
 35 40 45
 Gln Gln Ser Thr Gln Gln Pro Gln Gln Gln Pro Gln Pro Gln
 50 55 60
 Pro Gln Pro Gln Gln Glu Lys Ala Thr His Lys Pro Lys Lys Ser Ser
 65 70 75 80
 His Gln Ser Lys Asn Asn Asp Lys Leu Ala Gly Asp Glu Met His Glu
 85 90 95
 Trp Gln Gln Ser Trp Arg Arg Ile Met Lys Ser Ser Ile Val Tyr Phe
 100 105 110
 Glu Gly Asp Gln Gln Ser Leu Glu Tyr Arg Lys Ala His Lys Leu Leu
 115 120 125
 Arg Leu Val Gly Cys Lys Val Thr Pro Phe Tyr Asp Asn Asn Val Thr
 130 135 140
 Ile Ile Ile Ser Lys Arg Pro Tyr Asp Ser Lys Thr Glu Tyr Ser Pro
 145 150 155 160
 His Asp Ile Phe Ser Asn Val Ser Lys Ala Ser Ile Lys Val Trp Asn
 165 170 175
 Tyr Asp Lys Val Phe Arg Phe Leu Lys His Leu Gly Ile Asn Ile Gln
 180 185 190
 Thr Gly Val Asp Glu Leu Ala Val Asn Thr His Thr Ile Leu Pro Pro
 195 200 205
 Ser Leu Thr Asn Asn Asn Glu Lys Pro Asp Leu Tyr Asn Leu Leu Lys
 210 215 220
 Glu Glu Lys Ile Tyr Gly Ser Thr Asp Arg Asp Pro Asn Ala Lys Arg
 225 230 235 240
 Asp Asp Leu His Tyr Leu Gly Lys Asn Tyr Leu Tyr Val Tyr Asp Leu
 245 250 255
 Thr Gln Thr Val Arg Pro Ile Ala Ile Arg Glu Trp Ser Asp His Tyr
 260 265 270
 Pro Val Met Gln Leu Ser Leu Asp Gly Lys Cys Pro Phe Ile Glu Asp
 275 280 285
 Pro Thr Asp Gln Asn Ser Glu Arg Lys Arg Leu Lys Arg Leu Arg Lys
 290 295 300
 Phe Glu Ala Asn Gln Ala His Arg Glu Ala Leu Arg Leu Ala Thr Tyr
 305 310 315 320
 Lys Met Ile Asn Gly Ile Ser Met Ser Val His Gly Phe Thr Ala Thr
 325 330 335
 Ser Thr Ser Thr Asp Lys Val Asp Glu Glu Glu Asp Ser Thr Val Lys
 340 345 350
 Glu Pro Ser Glu Asp Pro Arg Phe Arg Gln Pro Leu Asn Arg Asn Ser
 355 360 365
 Ser Cys Met Gln Ser Lys Ala Phe Glu Ala Met Ala Ser Gly Tyr Asn
 370 375 380
 Gly Ala Ser Asn Ala Val Gln Pro Ser Met Asp Ser Asn Leu Asn Ser
 385 390 395 400
 Ala Ala Ala Met Ala Gly Gly Asn Gly Leu Gly Pro Ala Leu Ser Gln
 405 410 415
 Val Pro Ser Lys Gln Leu Asn Asn Leu Lys Arg Arg Ile Leu Met Lys
 420 425 430
 Lys Lys Thr Thr Asn Thr Thr Glu Lys Lys Asp Lys Glu His Ala Ser
 435 440 445
 Gly Tyr Cys Glu Asn Cys Arg Val Lys Tyr Thr Asn Phe Asp Glu His
 450 455 460
 Ile Met Thr Asn Arg His Arg Asn Phe Ala Cys Asp Asp Arg Asn Phe
 465 470 475 480
 Gln Asp Ile Asp Glu Leu Ile Ala Ser Leu Arg Glu Arg Lys Ser Leu
 485 490 495

Gly Asn Val Ile Ser Asn Gly Asp Tyr Val
 500 505

<210> 70

<211> 532

<212> PRT

<213> Candida albicans

<400> 70

Met Lys Pro Met Val Thr Thr Leu Tyr Asn Gly Lys Leu Pro Leu Ala
 1 5 10 15
 Leu Ala Asp Pro Asn Gly Ile Phe Thr Trp Cys Pro His Leu Asn Leu
 20 25 30
 Ile Phe Ile Ala Met Asn Lys Met Ser Ile Trp Cys Tyr Arg Met Asn
 35 40 45
 Gly Glu Arg Ile Tyr Ser Ile Asn Asn Lys Ser Ile Val Lys His Ile
 50 55 60
 Ala Phe Tyr Arg Glu Tyr Phe Cys Leu Ser Gly Thr Asp Asn Leu Ile
 65 70 75 80
 Lys Ile Tyr Asp Ser Asn Asn Gly Gln Leu Val Lys Val Leu Pro Gln
 85 90 95
 Glu Phe Asp Gly Val Glu Phe Val Gly Trp Asn Gly Thr Glu Tyr Arg
 100 105 110
 Val Ser Val Ser Met Pro Met Val Tyr Asp Leu Val Ser Glu Leu Asp
 115 120 125
 Tyr Leu Val Val Ser Asp Gly Lys Arg Met Ala Ile Thr Phe Asn Gln
 130 135 140
 Leu Leu Thr Val Asp Trp Glu Cys Glu Met Ser Val His Gln Gln Leu
 145 150 155 160
 Asn Arg Asp Leu Phe Asn Gln Val Tyr Val Ala Gly Asp Lys Leu Val
 165 170 175
 Arg Val Arg Phe Val Val Asp Asn Gln Lys Leu Tyr Thr Glu Gln Ile
 180 185 190
 Ile Lys Val Cys Gln Leu Ile Ser Leu Leu Glu Tyr Gly Glu Gln His
 195 200 205
 Ile Gln Lys Ile Lys Gly Leu Val Val Pro Phe Leu Ser Ala Met Asp
 210 215 220
 Arg Tyr Met Ser Asn Leu Glu Ser Glu Cys Gly Asp Leu Ala Gln Tyr
 225 230 235 240
 Leu Ser Asp Leu Val Val Ser Asn Ile Ile Pro Glu Phe Ser Lys Asp
 245 250 255
 Phe Trp Leu Asn Gln Tyr Gly Glu Arg Gly His Lys Arg Met Val Lys
 260 265 270
 Leu Ala Gly Val Tyr Glu Ser Cys Val Lys Asp Thr Tyr Gln His Leu
 275 280 285
 Val Ser Thr Thr Glu Arg Val Ile Ser Ile Val Gly Glu Leu Ile Gly
 290 295 300
 Val Ser Lys Trp Glu Gln Gly Leu Leu Ala Thr Thr Glu Leu Glu Ala
 305 310 315 320
 Leu Leu Asp Gln Ala Lys Ser Gln Leu Lys Phe Tyr Tyr Arg Phe Ile
 325 330 335
 Trp Asp Leu Gln Thr Glu Arg Gln Gln Val Ser Gln Phe Leu Val Trp
 340 345 350
 Thr Lys Ser Ile Ile Asp Met Leu Asn Asp Gln Glu Cys Asp Ile Ala
 355 360 365
 Tyr Ser Thr Thr Asp Val Leu Cys Phe Ile Asn Gly Ala Leu Thr Lys
 370 375 380

Ser Val Met Leu Lys Tyr Phe Asp Ile Lys Gly Val Pro Glu Thr Pro
 385 390 395 400
 Met Thr Asn Ile Ser Met Asp Leu Thr Thr Ile Gly Glu Tyr His Arg
 405 410 415
 Ser Arg Val Glu Val Glu Val Leu Gln Asn Ile Ser Leu Pro Ser Val
 420 425 430
 Tyr Thr Asn Leu Lys Leu Ala Gln Trp Glu Glu Val Val Val Thr Tyr
 435 440 445
 Gln Gln Gly Asn Ala Leu Val Ile Ala Asn Val Asp Gly Val Val Ser
 450 455 460
 Thr Val Gln Asp Val Tyr Ser Tyr Gln His Arg Gln Thr Asp Leu Val
 465 470 475 480
 Ala Leu Thr Ser Lys Ser Leu Leu Ile Ile Asp Ser Ser Ser Cys Ile
 485 490 495
 Pro Ile Ala Leu Pro Glu Thr Ser Phe Gln Pro Thr Lys Leu Ile Leu
 500 505 510
 Asn Gln Glu Tyr Gly Val Leu Leu Asp Ser Thr Arg Gln His Tyr Ser
 515 520 525
 Ile Phe Arg Met
 530

<210> 71

<211> 319

<212> PRT

<213> Candida albicans

<400> 71

Met Gly Lys Arg Arg Val Asp Glu Glu Ser Asp Ser Asp Ile Asp Val
 1 5 10 15
 Ser Ser Pro Asp Ser Glu Thr Glu Leu Glu Ser Thr His His His His
 20 25 30
 His His Gln Glu Gly Ala Thr Thr Ile Gln Glu Thr Val Asp Val Asp
 35 40 45
 Phe Asp Phe Phe Asp Leu Asn Pro Gln Ile Asp Phe His Ala Thr Lys
 50 55 60
 Asn Phe Leu Arg Gln Leu Phe Gly Asp Asp Asn Gly Glu Phe Asn Leu
 65 70 75 80
 Ser Glu Ile Ala Asp Leu Ile Leu Arg Glu Asn Ser Val Gly Thr Ser
 85 90 95
 Ile Lys Thr Glu Gly Met Glu Ser Asp Pro Phe Ala Ile Leu Ser Val
 100 105 110
 Ile Asn Leu Thr Asn Asn Leu Asn Val Ala Val Ile Lys Gln Leu Ile
 115 120 125
 Glu Tyr Ile Leu Asn Lys Thr Lys Ser Lys Thr Glu Phe Asn Ile Ile
 130 135 140
 Leu Lys Lys Leu Leu Thr Asn Gln Asn Asp Thr Thr Arg Asp Arg Lys
 145 150 155 160
 Phe Lys Thr Gly Leu Ile Ile Ser Glu Arg Phe Ile Asn Met Pro Val
 165 170 175
 Glu Val Ile Pro Pro Met Tyr Lys Met Leu Leu Gln Glu Met Glu Lys
 180 185 190
 Ala Glu Asp Ala His Glu Asn Glu Phe Asp Tyr Phe Leu Ile Ile Ser
 195 200 205
 Arg Val Tyr Gln Leu Val Asp Pro Val Glu Arg Glu Asp Glu Asp His
 210 215 220
 Glu Lys Glu Ser Asn Arg Lys Lys Lys Asn Lys Asn Lys Lys Lys Lys
 225 230 235 240

Leu Ala Asn Asn Glu Pro Lys Pro Ile Glu Met Asp Tyr Phe His Leu
 245 250 255
 Glu Asp Gln Ile Leu Glu Asn Thr Gln Phe Lys Gly Ile Phe Glu Tyr
 260 265 270
 Asn Asn Glu Asn Lys Gln Glu Thr Asp Ser Arg Arg Val Phe Thr Glu
 275 280 285
 Tyr Gly Ile Asp Pro Lys Leu Ser Leu Ile Leu Ile Asp Lys Asp Asn
 290 295 300
 Leu Ala Lys Ser Val Ile Glu Met Glu Gln Gln Phe Pro Pro Pro
 305 310 315

<210> 72

<211> 266

<212> PRT

<213> Candida albicans

<400> 72

Met Ala Gly Phe Lys Lys Asn Arg Glu Ile Leu Thr Gly Gly Lys Lys
 1 5 10 15
 Tyr Ile Gln Gln Lys Gln Lys Lys His Leu Val Asp Glu Val Val Phe
 20 25 30
 Asp Lys Glu Ser Arg His Glu Tyr Leu Thr Gly Phe His Lys Arg Lys
 35 40 45
 Leu Gln Arg Gln Lys Lys Ala Gln Glu Phe His Lys Glu Gln Glu Arg
 50 55 60
 Leu Ala Lys Ile Glu Glu Arg Lys Gln Leu Lys Gln Glu Arg Glu Arg
 65 70 75 80
 Asp Leu Gln Asn Gln Leu Gln Gln Phe Lys Lys Thr Ala Gln Glu Ile
 85 90 95
 Ala Ala Ile Asn Asn Asp Ile Gly Phe Asp Gln Ser Asp Asp Asn Asn
 100 105 110
 Asp Asn Asp Asn Glu Glu Trp Ser Gly Phe Gln Glu Asp Glu Glu Gly
 115 120 125
 Glu Gly Glu Glu Val Thr Asp Glu Asp Asp Glu Asp Lys Glu Lys Pro
 130 135 140
 Leu Lys Gly Ile Leu His His Thr Glu Ile Tyr Lys Gln Asp Pro Ser
 145 150 155 160
 Leu Ser Asn Ile Thr Asn Asn Gly Ala Ile Ile Asp Asp Glu Thr Thr
 165 170 175
 Val Val Val Glu Ser Leu Asp Asn Pro Asn Ala Val Asp Thr Glu Glu
 180 185 190
 Lys Leu Gln Gln Leu Ala Lys Leu Asn Asn Val Asn Leu Asp Lys Ser
 195 200 205
 Asp Gln Ile Leu Glu Lys Ser Ile Glu Arg Ala Lys Asn Tyr Ala Val
 210 215 220
 Ile Cys Gly Val Ala Lys Pro Asn Pro Ile Lys Gln Lys Lys Lys Lys
 225 230 235 240
 Phe Arg Tyr Leu Thr Lys Ala Glu Arg Arg Glu Asn Val Arg Lys Glu
 245 250 255
 Lys Ser Lys Ser Lys Ser Lys Gly Lys Lys
 260 265

<210> 73

<211> 332

<212> PRT

<213> Candida albicans

<400> 73

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Met Ser Thr Val Tyr Tyr Lys Lys Leu Asp Lys Leu Gln Phe Gln Ile
 1           5           10           15
Tyr Asp Leu Phe Ser Ser Leu Leu Gln Leu Ser Glu Ala Glu Asp Glu
          20           25           30
Ser Val Tyr Lys Ala Ser Phe Asp Asp Thr Val Gln Glu Ile Asp Ser
 35           40           45
Leu Leu Ile Ala Phe Lys Asp Leu Leu Arg Leu Leu Arg Pro Lys Asp
 50           55           60
Lys Ser Asn Lys Phe Asp Thr Tyr Glu Leu Lys Phe His Ser Leu Lys
 65           70           75           80
His Lys Leu Arg Glu Leu Gln Val Phe Ile Asn Asp Gln Gln Gln Asp
          85           90           95
Lys Leu His Glu Tyr Arg Ile Lys His Phe His Leu Gln Asp Ser Pro
          100          105          110
Val Asp Thr Ile Asn Asn Glu Phe Ala Arg Asp Gln Leu Phe Ala Asp
          115          120          125
Arg Ser Thr Lys Lys Thr Lys Lys Glu Met Glu Ala Ser Ile Asn Gln
          130          135          140
Gln Ile Val Ser Gln Asn Lys Gln Ile Thr Lys Ser Leu Gln Ala Ser
 145          150          155          160
Arg Gln Leu Leu Ser Ala Gly Ile Leu Gln Ser Glu Leu Asn Ile Asp
          165          170          175
Asn Ile Asp Gln Gln Thr Lys Asp Leu Tyr Lys Leu Asn Glu Gly Phe
          180          185          190
Ile Gln Phe Asn Asp Leu Leu Asn Arg Ser Lys Lys Ile Val Lys Phe
          195          200          205
Ile Glu Lys Gln Asp Lys Ala Asp Arg Gln Arg Ile Tyr Leu Ser Met
          210          215          220
Gly Phe Phe Ile Leu Cys Ser Trp Val Val Tyr Arg Arg Ile Leu
 225          230          235          240
Arg Arg Pro Leu Lys Ile Phe Leu Trp Ser Phe Phe Lys Ile Phe Asn
          245          250          255
Ile Phe Asn Trp Leu Leu Gly Gly Gly Arg Ser Lys Gly Leu Ser Ala
          260          265          270
Ser Asp Met Ile Val Ser Ser Val Ile Ala Ala Thr Thr Glu Ile Val
          275          280          285
Asp Tyr Glu Ala Thr Lys Thr Leu Leu Asp Thr Leu Ser Asn Ala Val
          290          295          300
Asp Ser Asn Thr Ala Ile Asp Thr Leu Ala Met Val Val Glu Ser Leu
 305          310          315          320
Thr Thr Ser Ser Met Glu His Ile Val Asp Glu Leu
          325          330

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<210> 74

<211> 273

<212> PRT

<213> Candida albicans

<400> 74

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Met Thr Asp Ser Ser Ala Thr Gly Phe Ser Lys His Gln Glu Ser Ala
 1           5           10           15
Ile Val Ser Asp Ser Glu Gly Asp Ala Ile Asp Ser Glu Leu His Met
          20           25           30
Ser Ala Asn Pro Pro Leu Leu Arg Arg Ser Ser Ser Leu Phe Ser Leu
          35           40           45
Ser Ser Lys Asp Asp Leu Pro Lys Pro Asp Ser Lys Glu Tyr Leu Lys
          50           55           60

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Phe Ile Asp Asp Asn Arg His Phe Ser Met Ile Arg Asn Leu His Met
 65 70 75 80
 Ala Asp Phe Ile Thr Leu Leu Asn Gly Phe Ser Gly Phe Tyr Ser Ile
 85 90 95
 Ile Ser Cys Leu Arg Tyr Thr Leu Thr Gly Gln Thr His Tyr Val Gln
 100 105 110
 Arg Ala His Phe Phe Ile Leu Leu Gly Leu Phe Phe Asp Phe Phe Asp
 115 120 125
 Gly Arg Val Ala Arg Leu Arg Asn Lys Ser Ser Leu Met Gly Gln Glu
 130 135 140
 Leu Asp Ser Leu Ala Asp Leu Val Ser Phe Gly Val Ser Pro Ala Thr
 145 150 155 160
 Ile Ala Phe Ala Ile Gly Phe Arg Thr Thr Val Asp Val Leu Phe Leu
 165 170 175
 Ala Phe Trp Val Leu Cys Gly Leu Thr Arg Leu Ala Arg Phe Asn Ile
 180 185 190
 Ser Val Asn Asn Ile Pro Lys Asp Lys His Gly Lys Ser Gln Tyr Phe
 195 200 205
 Glu Gly Leu Pro Ile Pro Thr Asn Leu Phe Trp Val Gly Phe Met Ala
 210 215 220
 Leu Leu Val Tyr Lys Asp Trp Ile His Asp Asn Leu Pro Phe Gly Ile
 225 230 235 240
 Val Phe Gln Asp Thr Ser Phe Glu Phe His Leu Val Thr Ile Gly Phe
 245 250 255
 Val Leu Gln Gly Cys Ala Glu Ile Ser Lys Ser Leu Lys Ile Pro Lys
 260 265 270
 Pro

<210> 75
 <211> 1175
 <212> PRT
 <213> Candida albicans

<400> 75
 Met Ala Lys Arg Lys Leu Glu Glu Asn Asp Ile Ser Thr Ile Glu Asp
 1 5 10 15
 Asp Glu Phe Lys Ser Phe Ser Asp Arg Asp Glu Gln Ile Asp Glu Leu
 20 25 30
 Ser Asn Gly His Ala Lys His Arg Glu Asn Asn Ala Gln Glu Ser Asp
 35 40 45
 Asp His Ser Ala Ser Glu Asp Asp Asp Asp Glu Asp Asp Glu Glu Glu
 50 55 60
 Gly Glu Lys Ser Val Gln Pro Pro Asn Lys Lys Gln Lys Lys Gln Leu
 65 70 75 80
 Ser Ala Gln Asp Val Gln Val Ala Arg Glu Thr Ala Glu Leu Phe Lys
 85 90 95
 Ser Asn Ile Phe Lys Leu Gln Ile Asp Glu Leu Met Lys Glu Val Lys
 100 105 110
 Val Lys Lys Ala His Glu Glu Lys Ile Glu Lys Val Leu His Arg Leu
 115 120 125
 His Asp Leu Ile Lys Gln Val Pro Pro Val Glu Asn Leu Thr Leu Gln
 130 135 140
 Gln Ala Glu Gln His Phe Asn Pro Lys Lys Leu Val Ile Pro Phe Pro
 145 150 155 160
 Asp Pro Lys Pro Thr Lys Val Asn Tyr Arg Phe Ser Tyr Leu Pro Ser
 165 170 175

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Gly Asp Leu Ser Leu Val Gly Ser Tyr Gly Leu Lys Thr Ala Ile Asn
      180              185              190
Gln Pro His Gly Gln Ser Ile Glu Val Ala Leu Thr Met Pro Lys Glu
      195              200              205
Leu Phe Gln Pro Lys Asp Tyr Leu Asn Tyr Arg Ala Leu Tyr Lys Lys
      210              215              220
Ser Phe Tyr Leu Ala Tyr Leu Gly Glu Asn Leu Ile His Leu Ser Lys
      225              230              235              240
Lys Asn Asn Leu Pro Ile Lys Val Ser Tyr Gln Phe Phe Asn Asp Asp
      245              250              255
Val Leu Asn Pro Val Leu Lys Ile Glu Ser Ile Gln Thr Glu Asn Pro
      260              265              270
Glu Asp Leu Thr Phe Thr Lys Thr Lys Ile Ala Ile Asn Leu Ile Val
      275              280              285
Ala Phe Pro Phe Gly Val Phe Asp Ser Lys Lys Leu Leu Pro Asp Lys
      290              295              300
Asn Cys Ile Arg Val Gln Ser Asp Thr Glu Thr Leu Pro Pro Thr Pro
      305              310              315              320
Leu Tyr Asn Ser Ser Val Leu Ser Gln Thr Ser Tyr Asp Tyr Tyr Leu
      325              330              335
Lys Tyr Leu Tyr Thr Thr Lys Lys Ser Thr Glu Ala Phe Lys Asp Ala
      340              345              350
Cys Met Leu Gly Lys Leu Trp Leu Gln Gln Arg Gly Phe Asn Ser Ser
      355              360              365
Leu Asn Asn Gly Gly Phe Gly His Phe Glu Phe Ala Ile Leu Met Ser
      370              375              380
Ala Leu Leu Asn Gly Gly Gly Leu Asn Gly Asn Lys Ile Leu Leu His
      385              390              395              400
Gly Phe Ser Ser Tyr Gln Leu Phe Lys Gly Thr Ile Lys Tyr Leu Ala
      405              410              415
Thr Met Asp Leu Asn Gly Gly Tyr Leu Ser Phe Ser Ser Leu Ile Gly
      420              425              430
Glu Asn Ile Ala Ser Lys Tyr Lys Ser Asp Gly Phe Asn Val Pro Thr
      435              440              445
Ile Phe Asp Lys Asn Thr Lys Leu Asn Ile Leu Trp Lys Met Thr Lys
      450              455              460
Ser Ser Tyr Lys Ser Leu Gln Leu Gln Ala Gln Gln Thr Leu Glu Leu
      465              470              475              480
Leu Asn Asp Val Val Lys Asp Arg Phe Asp Ala Ile Leu Leu Gln Lys
      485              490              495
Ser Asp Phe Asp Pro Met Arg Tyr Asp Ile Val Phe Lys Leu Ser Ala
      500              505              510
Pro Glu Glu Leu Tyr Asp Ser Phe Gly Pro Leu Glu Lys Ile Ala Tyr
      515              520              525
Ile Thr Phe Asp Asn Tyr Phe Lys Ser Arg Leu Phe Ala Ile Leu Thr
      530              535              540
Lys Ala Leu Gly Glu Arg Ile Glu Ser Ile Val Ile Lys Asn Glu His
      545              550              555              560
Pro Ser Asn Thr Phe Ala Ile His Lys Arg Lys Pro Ser His Thr Ser
      565              570              575
Ser Thr Phe Val Ile Gly Leu Gln Leu Asn Pro Glu Glu Cys Asp Lys
      580              585              590
Leu Val Thr Lys Gly Pro Asn Asn Glu Asp Lys Asp Ala Gly Ile Lys
      595              600              605
Phe Arg Ser Phe Trp Gly Asn Lys Ala Ser Leu Arg Arg Phe Lys Asp
      610              615              620
Gly Ser Ile Gln His Cys Val Val Trp Asn Ile Lys Asp Gln Glu Pro
      625              630              635              640

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Val Val Met Asn Ile Ile Lys Tyr Ala Leu Asp Thr His Leu Gln Ser
 645 650 655
 Glu Ile Ser Gln His Leu Ala Ser Ser Ile Ser Tyr Phe Asp Lys Lys
 660 665 670
 Leu Pro Val Pro Leu Leu Pro Ser Ala Thr Asn Gln Val Ile Thr Ser
 675 680 685
 Leu Ser Ser Phe Thr Ala Leu Arg Asn Ser Phe Glu Asn Leu Ser Lys
 690 695 700
 Val Leu Thr Asn Leu Glu Leu Pro Leu Ser Val Lys Thr Val Leu Pro
 705 710 715 720
 Ala Ser Ser Gly Leu Arg Tyr Thr Ser Val Leu Gln Pro Val Pro Phe
 725 730 735
 Ala Ala Ser Asn Pro Asp Phe Trp Asn Tyr Cys Val Leu Gln Phe Glu
 740 745 750
 Thr Ser Thr Arg Trp Pro Asp Glu Leu Ser Ala Leu Glu Lys Thr Lys
 755 760 765
 Thr Ala Phe Leu Leu Lys Ile Ser Glu Glu Leu Ala Glu Thr Glu Tyr
 770 775 780
 Asn Ser Phe Ile Ser Lys Asp Glu Ser Val Pro Phe Asn Glu Asn Ile
 785 790 795 800
 Thr Leu Leu Asn Ile Leu Thr Pro Glu Gly Tyr Gly Phe Arg Ile Arg
 805 810 815
 Ala Phe Thr Glu Arg Asp Glu Leu Leu Tyr Leu Arg Ala Val Ser Asn
 820 825 830
 Ala Asp Lys Gln Lys Ala Leu Val Gln Asp Val Tyr Leu Lys Phe Asn
 835 840 845
 Glu Lys Tyr Met Gly Ser Val Lys His Thr Arg Ser Val Thr Gln Leu
 850 855 860
 Ala Gln His Phe His Phe Tyr Ser Pro Thr Val Arg Phe Phe Lys Gln
 865 870 875 880
 Trp Leu Asp Ser Gln Leu Leu Leu Gln His Phe Ser Glu Glu Leu Val
 885 890 895
 Glu Leu Ile Ala Leu Lys Pro Phe Val Asp Pro Ala Pro Tyr Ser Ile
 900 905 910
 Pro His Ser Val Glu Asn Gly Phe Leu Gln Ile Leu Asn Phe Leu Ala
 915 920 925
 Ser Trp Asn Trp Lys Glu Asp Pro Leu Val Leu Asp Leu Val Lys Ser
 930 935 940
 Ser Ala Asp Asp Asp Ile Lys Leu Ser Asp Lys Leu Thr Ile Gln Ala
 945 950 955 960
 His Arg Ile Ile Glu Gln Asn Phe Glu Lys Ile Arg Lys Thr Asp Pro
 965 970 975
 Ser Gly Ile Lys Thr Gln Tyr Phe Ile Gly Ser Lys Asp Asp Pro Ser
 980 985 990
 Gly Ile Leu Trp Ser His Asn Leu Thr Leu Pro Ile Ser Thr Arg Leu
 995 1000 1005
 Thr Ala Leu Ser Arg Ala Ala Ile Gln Leu Leu Arg Lys Glu Gly Ile
 1010 1015 1020
 Thr Glu Thr Asn Leu Asp Leu Ile Phe Thr Pro Ala Leu Gln Asp Tyr
 1025 1030 1035 1040
 Asp Phe Thr Ile Lys Val Lys Ala Asn Asn Val Thr Thr Ser Ser Gly
 1045 1050 1055
 Ile Leu Pro Pro Asn Thr Phe Lys Asn Leu Ile Gln Pro Leu Thr Ser
 1060 1065 1070
 Phe Pro Asp Asp Ile Thr Thr Lys Tyr Asp Leu Val Gln Gly Tyr Val
 1075 1080 1085
 Asp Glu Leu Asn Lys Lys Phe Gly Asn Ala Ile Ile Phe Ser Ser Lys
 1090 1095 1100

Lys Phe Thr Gly Leu Cys Lys Asn Asn Glu Asn Val Ile Gly Gly Ile
 1105 1110 1115 1120
 Phe Val Pro Thr Asn Leu Thr Lys Lys Lys Phe Arg Val Asn Leu Gly
 1125 1130 1135
 Ile Asn Val Lys Pro Leu Asp Asp Lys Gly Asp Glu Val Ile Ile Asn
 1140 1145 1150
 Thr Ser Ser Ile Tyr Asp Glu Ile Glu Leu Leu Gly Gly Asp Leu Ile
 1155 1160 1165
 Lys Ala Phe Asp Lys Arg Lys
 1170 1175

<210> 76

<211> 759

<212> PRT

<213> Candida albicans

<400> 76

Met Ala Lys Lys Arg Arg Ala Ala Ile Leu Pro Thr Asn Ile Ile Leu
 1 5 10 15
 Leu Gln Asn Val Val Arg Arg Asp Pro Glu Ser Tyr His Glu Glu Phe
 20 25 30
 Leu Gln Gln Phe Ser His Tyr Glu Ser Leu Arg Asp Leu Tyr Leu Ile
 35 40 45
 Asn Pro Thr Gly Val Asp Ala Asn Ser Thr Thr Glu Phe Ile Asp Leu
 50 55 60
 Ile Gly Phe Met Ser Ala Val Cys Asn Cys Tyr Pro Lys Glu Thr Ala
 65 70 75 80
 Asn Phe Pro Asn Glu Leu Lys Glu Ile Leu Leu Asn Asn His Arg Asp
 85 90 95
 Leu Thr Pro Glu Leu Arg Glu Lys Ile Ile Gln Cys Leu Thr Met Leu
 100 105 110
 Arg Asn Lys Asp Ile Ile Ser Ala Glu Met Leu Ile Gln Thr Ile Phe
 115 120 125
 Pro Leu Leu Ile Thr Ser Asn Ala Gly Gln Gln Val Lys Gln Met Arg
 130 135 140
 Lys Gln Ile Tyr Ser Thr Leu Ile Ala Leu Leu Lys Ser Val Asn Thr
 145 150 155 160
 Gly Thr Lys Asn Gln Lys Leu Asn Arg Ser Thr Gln Ala Leu Leu Phe
 165 170 175
 Asn Leu Leu Glu Gln Arg Asp Asn Gln Gly Leu Trp Ala Thr Lys Leu
 180 185 190
 Thr Arg Glu Leu Trp Arg Arg Gly Ile Trp Asp Asp Ser Arg Thr Val
 195 200 205
 Glu Ile Met Thr Gln Ala Ala Leu His Pro Asp Val Lys Val Ala Val
 210 215 220
 Ala Gly Ala Arg Phe Phe Leu Gly Ala Asp Lys Glu Arg Glu Asp Asn
 225 230 235 240
 Phe Glu Glu Ser Ser Asp Glu Asp Gly Phe Asp Met Asn Glu Leu Arg
 245 250 255
 His Lys Met Gln Ile Asn Lys Lys Thr Ser Lys Arg Gly Lys Lys Leu
 260 265 270
 Glu Gln Ala Val Lys Ala Met Lys Lys Asn Asn Ser Lys His Ser
 275 280 285
 Ala Thr Tyr Leu Asn Phe Ser Ala Ile His Leu Leu Arg Asp Pro Gln
 290 295 300
 Gly Phe Ala Glu Gln Met Phe Asp Asn His Leu Ser Ser Lys Asn Ser
 305 310 315 320

Asn Lys Phe Asp Leu Asp Gln Lys Ile Leu Phe Met Asn Leu Ile Ser
 325 330 335
 Arg Leu Ile Gly Thr His Lys Leu Ile Val Leu Gly Val Tyr Thr Phe
 340 345 350
 Phe Leu Lys Tyr Leu Thr Pro Lys Gln Arg Asn Val Thr Gln Ile Met
 355 360 365
 Ala Ala Ala Ala Gln Ala Ser His Asp Leu Val Pro Pro Glu Ser Ile
 370 375 380
 Gln Ile Val Val Arg Lys Ile Ala Asp Glu Phe Val Ser Asp Gly Val
 385 390 395 400
 Ala Ala Glu Val Ala Ser Ala Gly Ile Asn Thr Ile Arg Glu Ile Leu
 405 410 415
 Ala Arg Ala Pro Leu Ala Ile Asp Ala Pro Leu Leu Gln Asp Leu Thr
 420 425 430
 Glu Tyr Lys Gly Ser Lys Ser Lys Ala Val Met Met Ala Ala Arg Ser
 435 440 445
 Leu Ile Ser Leu Tyr Arg Glu Val Ala Pro Glu Met Leu Leu Lys Lys
 450 455 460
 Asp Arg Gly Lys Val Ala Ser Ile Glu Leu Gln Lys Gly Glu Lys Ser
 465 470 475 480
 Gly Leu Pro Gln Tyr Gly Val Glu Asn Asn Val Thr Ser Ile Pro Gly
 485 490 495
 Ile Glu Leu Leu Ala Lys Trp Lys Lys Glu Gln Gly Leu Asp Ser Arg
 500 505 510
 Glu Asp Glu Glu Asp Asp Ala Asn Trp Glu Val Asp Asp Glu Asp
 515 520 525
 Ala Ser Asp Ile Glu Gly Asp Trp Ile Asp Val Glu Ser Asp Lys Glu
 530 535 540
 Ile Asn Ile Ser Asp Ser Asp Asp Asn Glu Glu Asp Glu Gln Glu
 545 550 555 560
 Gln Glu Pro Glu Lys Gly Lys Ala Lys Ile Gly Lys Ala Glu Asp Asn
 565 570 575
 Glu Asp Glu Val Ser Asp Leu Glu Leu Ser Ser Asp Asp Asp Glu
 580 585 590
 Asp Ser Glu Glu Asn Lys Asp Gly Lys Ala Val Ala Asp Ser Glu Glu
 595 600 605
 Pro Pro Thr Lys Lys Gln Lys Ile Arg Asn Glu Asn Ala Asp Ile Asn
 610 615 620
 Ala Glu Gln Ala Met Asn Glu Leu Leu Ser Ser Arg Ile Leu Thr Pro
 625 630 635 640
 Ala Asp Phe Ala Lys Leu Glu Glu Leu Arg Thr Glu Ala Gly Val Ser
 645 650 655
 Lys Ile Met Gly Ile Ser Asn Glu Glu Ala Val Asp Ser Thr Ser Leu
 660 665 670
 Val Gly Lys Val Lys Tyr Lys Gln Leu Arg Glu Glu Arg Ile Ala His
 675 680 685
 Ala Lys Glu Gly Lys Glu Asp Arg Glu Lys Phe Gly Ser Arg Lys Gly
 690 695 700
 Lys Arg Asp Thr Pro His Ser Thr Thr Asn Lys Glu Lys Ala Arg Lys
 705 710 715 720
 Lys Asn Phe Val Met Met Ile His Lys Lys Ala Val Gln Gly Lys Gln
 725 730 735
 Lys Leu Ser Leu Arg Asp Arg Gln Arg Val Leu Arg Ala His Ile Thr
 740 745 750
 Lys Gln Lys Lys Lys Gly Leu
 755

<210> 77

<211> 528

<212> PRT

<213> *Candida albicans*

<400> 77

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Met Ala Ile Val Glu Thr Val Ile Asp Gly Ile Asn Tyr Phe Leu Ser
 1           5           10          15
Leu Ser Val Thr Gln Gln Ile Ser Ile Leu Leu Gly Val Pro Phe Val
      20           25           30
Tyr Asn Leu Val Trp Gln Tyr Leu Tyr Ser Leu Arg Lys Asp Arg Ala
      35           40           45
Pro Leu Val Phe Tyr Trp Ile Pro Trp Phe Gly Ser Ala Ala Ser Tyr
      50           55           60
Gly Gln Gln Pro Tyr Glu Phe Phe Glu Ser Cys Arg Gln Lys Tyr Gly
65           70           75           80
Asp Val Phe Ser Phe Met Leu Leu Gly Lys Ile Met Thr Val Tyr Leu
      85           90           95
Gly Pro Lys Gly His Glu Phe Val Phe Asn Ala Lys Leu Ser Asp Val
      100          105          110
Ser Ala Glu Glu Ala Tyr Lys His Leu Thr Thr Pro Val Phe Gly Lys
      115          120          125
Gly Val Ile Tyr Asp Cys Pro Asn Ser Arg Leu Met Glu Gln Lys Lys
      130          135          140
Phe Ala Lys Phe Ala Leu Thr Thr Asp Ser Phe Lys Arg Tyr Val Pro
145          150          155          160
Lys Ile Arg Glu Glu Ile Leu Asn Tyr Phe Val Thr Asp Glu Ser Phe
      165          170          175
Lys Leu Lys Glu Lys Thr His Gly Val Ala Asn Val Met Lys Thr Gln
      180          185          190
Pro Glu Ile Thr Ile Phe Thr Ala Ser Arg Ser Leu Phe Gly Asp Glu
      195          200          205
Met Arg Arg Ile Phe Asp Arg Ser Phe Ala Gln Leu Tyr Ser Asp Leu
      210          215          220
Asp Lys Gly Phe Thr Pro Ile Asn Phe Val Phe Pro Asn Leu Pro Leu
225          230          235          240
Pro His Tyr Trp Arg Arg Asp Ala Ala Gln Lys Lys Ile Ser Ala Thr
      245          250          255
Tyr Met Lys Glu Ile Lys Ser Arg Arg Glu Arg Gly Asp Ile Asp Pro
      260          265          270
Asn Arg Asp Leu Ile Asp Ser Leu Leu Ile His Ser Thr Tyr Lys Asp
      275          280          285
Gly Val Lys Met Thr Asp Gln Glu Ile Ala Asn Leu Leu Ile Gly Ile
      290          295          300
Leu Met Gly Gly Gln His Thr Ser Ala Ser Thr Ser Ala Trp Phe Leu
305          310          315          320
Leu His Leu Gly Glu Lys Pro His Leu Gln Asp Val Ile Tyr Gln Glu
      325          330          335
Val Val Glu Leu Leu Lys Glu Lys Gly Gly Asp Leu Asn Asp Leu Thr
      340          345          350
Tyr Glu Asp Leu Gln Lys Leu Pro Ser Val Asn Asn Thr Ile Lys Glu
      355          360          365
Thr Leu Arg Met His Met Pro Leu His Ser Ile Phe Arg Lys Val Thr
      370          375          380
Asn Pro Leu Arg Ile Pro Glu Thr Asn Tyr Ile Val Pro Lys Gly His
385          390          395          400
Tyr Val Leu Val Ser Pro Gly Tyr Ala His Thr Ser Glu Arg Tyr Phe
      405          410          415

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Asp Asn Pro Glu Asp Phe Asp Pro Thr Arg Trp Asp Thr Ala Ala Ala
 420 425 430
 Lys Ala Asn Ser Val Ser Phe Asn Ser Ser Asp Glu Val Asp Tyr Gly
 435 440 445
 Phe Gly Lys Val Ser Lys Gly Val Ser Ser Pro Tyr Leu Pro Phe Gly
 450 455 460
 Gly Gly Arg His Arg Cys Ile Gly Glu Gln Phe Ala Tyr Val Gln Leu
 465 470 475 480
 Gly Thr Ile Leu Thr Thr Phe Val Tyr Asn Leu Arg Trp Thr Ile Asp
 485 490 495
 Gly Tyr Lys Val Pro Asp Pro Asp Tyr Ser Ser Met Val Val Leu Pro
 500 505 510
 Thr Glu Pro Ala Glu Ile Ile Trp Glu Lys Arg Glu Thr Cys Met Phe
 515 520 525

<210> 78

<211> 433

<212> PRT

<213> Candida albicans

<400> 78

Met Pro Ser His Val Thr Asn Val Tyr Asn Asp Ile Asp Asp Gly Met
 1 5 10 15
 Leu Leu Ser Ser Leu Ser Leu Asn Glu Arg Ser Asn Asp Arg Arg Gly
 20 25 30
 Leu Glu Ile Glu Glu Val Tyr Asp Ser Ser Phe Asp Asp Pro Met Asp
 35 40 45
 Ile Asp Asp Thr Gly Glu Leu Ser Asn His Met Asp Ile Asp Asp Thr
 50 55 60
 Thr Phe Glu Ile Asp His Val Ala Ser Asp Asn Tyr Ala Asn Lys Arg
 65 70 75 80
 Glu Asp Asp Asn Asp Thr Asn Asn Glu Glu Glu Arg Arg Glu Asp Gly
 85 90 95
 Leu Phe Ser Leu Leu Ser Pro Thr Leu Met Gly Ala Lys Leu Ala Ile
 100 105 110
 Lys Lys Pro Leu Leu Leu Met Pro Pro Pro Thr Val Ser Glu Gln Ser
 115 120 125
 Asp Ser Lys Thr Glu Ser Ala Ser Ser Val Asp Tyr Glu Tyr Asp Thr
 130 135 140
 Ser Ser Phe Lys Pro Met Lys Ser Asn Gly Leu Ile Thr Arg Lys Thr
 145 150 155 160
 Asn Ser Ser Thr Phe Gln Pro Ser Asn Ile Asp Ser Phe Leu Phe His
 165 170 175
 Ser Asp Gly Ile Ser Ser Gly Gln Ser Leu Gly Gly Tyr Gln Asp Leu
 180 185 190
 His Ser Asn Tyr Gln Gln Pro Val Thr Ile His Asn His His His
 195 200 205
 Tyr Tyr Tyr Tyr Asn Lys Asp Glu Ser Val Pro Ser Pro Pro Ser Asn
 210 215 220
 Asn Asn Leu Gln Ser Leu Glu His Glu Gln Arg Asn Leu Gln Met Gln
 225 230 235 240
 Gln Tyr Lys Gln Gln Leu Glu Glu His Gln Leu Tyr Leu Gln Glu Tyr
 245 250 255
 Lys Arg Asn Asn Gln Ile Leu Leu Pro Ser Pro Trp Gln His Asn Ile
 260 265 270
 Ser Pro Ile Glu Arg Val Pro Tyr Leu Leu Met Ser Tyr Leu Gln Met
 275 280 285

Leu Ile Asn Phe Ile Ala Ser Leu Tyr Gly Val Tyr Leu Val Tyr Cys
 290 295 300
 Leu Phe Arg Thr Ile Asn Thr Asp Ile Lys Thr Lys Ile Glu Glu Gln
 305 310 315 320
 Gln Thr Asn Leu Ile Ile Ser Ile Glu Ser Cys Arg Arg Ser Tyr Tyr
 325 330 335
 Gln Asn Gly Cys Asp Asp Lys Asp Asn Leu Val Pro Leu Leu Val Ser
 340 345 350
 Lys Cys Gln Lys Phe Glu Lys Cys Met Lys Gln Asp Pro Tyr Lys Leu
 355 360 365
 Ser Asn Val Ser Ile Met Ser Ala Glu Ile Ile Gly Met Ile Ile Asn
 370 375 380
 Ser Leu Ile Glu Pro Leu Ser Leu Lys Phe Tyr Leu Phe Met Leu Ala
 385 390 395 400
 Phe Ile Leu Ile Ile Phe Ala Cys Asn Phe Thr Phe Gly Tyr Ile Arg
 405 410 415
 Ala Lys Ala Tyr Tyr Gly Gly Ser Met Lys Tyr Ser Leu Asp Lys Leu
 420 425 430
 Asp

<210> 79
 <211> 263
 <212> PRT
 <213> Candida albicans

<400> 79
 Met Glu Ser Leu Asp Glu Ile Gln Trp Lys Ser Pro Glu Phe Ile Gln
 1 5 10 15
 Glu Arg Gly Leu Asn Thr Asn Asn Val Leu Glu Tyr Phe Ser Leu Ser
 20 25 30
 Pro Phe Tyr Asp Arg Thr Ser Asn Asn Gln Val Leu Met Met Gln Phe
 35 40 45
 Gln Tyr Gln Gln Ile Gln Ile Pro Pro Gly Val Ser Phe His Gln Tyr
 50 55 60
 Phe Gln Ser Arg Leu Ser Glu Met Thr Gly Ile Glu Phe Val Ile Ala
 65 70 75 80
 Tyr Thr Lys Glu Pro Asp Phe Trp Ile Ile Arg Lys Gln Lys Arg Gln
 85 90 95
 Asp Pro Gln Asn Thr Val Thr Leu Gln Asp Tyr Tyr Ile Ile Gly Ala
 100 105 110
 Asn Val Tyr Gln Ala Pro Arg Ile Tyr Asp Val Leu Ser Ser Arg Leu
 115 120 125
 Leu Ala Ser Val Leu Ser Ile Lys Asn Ser Thr Asp Leu Leu Asn Asp
 130 135 140
 Met Thr Ser Tyr His Ile Ser Asp Gly Gly His Ser Tyr Ile Asn Ser
 145 150 155 160
 Ile His Gly Ser Ser Ser Lys Pro Ser Gln Ser Ser Ala Val Ser Lys
 165 170 175
 Pro Ser Ser Thr Asn Thr Gly Thr Asn Ala Thr Thr Thr Pro Ile Thr
 180 185 190
 Leu Thr Thr Pro Ser Gly Ala Thr Val Pro Ser Thr Val Ser Asn Gly
 195 200 205
 Ile Ser Thr Ser Thr Glu Ile Ala Ser Gly Val Phe Asp Thr Leu Leu
 210 215 220
 Asn Asp Val Val Met Asn Asp Asp His Leu Tyr Ile Asp Glu Ile Pro
 225 230 235 240

Leu Tyr Gly Glu Gly Ser Thr Leu Glu Arg Leu Gly Leu Lys Gly Asn
 245 250 255
 Lys Asp Ala Gly Leu Ser Leu
 260

<210> 80
 <211> 363
 <212> PRT
 <213> Candida albicans

<400> 80
 Met Ser Ser Ser Gln Ala Arg Lys Ala Leu Gln Asp Val Ile Pro Asn
 1 5 10 15
 Tyr Leu Gly Glu Phe Thr Pro Lys Leu Leu Asp Tyr Ile Asn Ser Leu
 20 25 30
 Tyr Gln Leu Ser Leu Arg Lys Gln Ala Ile Leu Pro Asn Lys Ser Glu
 35 40 45
 Ile Ala Arg Phe His Leu Cys Ala Val Val Ile Val Glu Lys Tyr Lys
 50 55 60
 Gln Ser Phe Glu Leu Pro Thr Pro Asp Val Ser Arg Ile Pro Thr Gln
 65 70 75 80
 Pro Lys Val Ala Ala Lys Leu Leu Asp Thr Phe Arg Glu Leu Ile Glu
 85 90 95
 Gln Ile Ser Ala Ala Ser Thr Pro Val Ser Ser Pro Lys Lys Val Lys
 100 105 110
 Pro Pro Ser Gln Ser Pro Ser Thr Pro Thr Lys Ser Arg Thr Ser Lys
 115 120 125
 Glu Asn Leu Lys Ser Gly Ser Pro Leu Lys Arg Leu Arg Ala Glu Met
 130 135 140
 Leu Gln Glu Asp Gln Val Asn Gly Asn Ser Pro Asp Gly Gln Leu Lys
 145 150 155 160
 Asp Val Asp Ser Pro Phe Asn Pro Lys Lys Arg Lys Glu Ser Lys Ala
 165 170 175
 Gly Thr Pro Thr His Lys Val Tyr Lys Tyr Asp Lys Lys His Val Ser
 180 185 190
 Ile Ala Asp Phe Ile Ala Phe Cys Asn Thr Phe Leu Ile Pro Gly Asp
 195 200 205
 Ile Thr Ala Lys Met Val Gly Thr Phe Leu Thr His Gln His Lys Phe
 210 215 220
 Leu Lys Lys Ser Asp Trp Ser Leu Ala Cys Gly Met Val Tyr Ala Ala
 225 230 235 240
 Tyr Ile Arg Ile Asn Asn Arg Leu Leu Ala Gln Ser Val Gly Thr Lys
 245 250 255
 Ser Glu Phe Thr Lys Gln Leu Leu Gln Tyr Gln Lys Gly Gly Leu Ser
 260 265 270
 Leu Gly Ala Met Gln Ser Trp Cys Gly Ile Ile Glu Glu Trp Ile Gln
 275 280 285
 Asp Glu Pro Trp Ile Gln Glu Ile Glu Lys Thr Tyr Ala Tyr Gly Ser
 290 295 300
 Lys Thr Ala Glu Glu Thr Arg Asn Ser Phe Glu Arg Lys Ala Lys Ile
 305 310 315 320
 Gly Glu Gly Trp Asp Leu Met Glu Gln Phe Gly Ala Met Ile His Gly
 325 330 335
 Glu Thr Ile Ser Leu Ser Ser His Gln Glu Glu Tyr Tyr Lys Asn Trp
 340 345 350
 Arg Lys Glu Ala Leu Glu Lys Cys Asp Gln Leu
 355 360

<210> 81
 <211> 871
 <212> PRT
 <213> Candida albicans

<400> 81
 Met Asn Thr Phe Ser Ser Pro Pro Asn Val Ile Arg Glu Tyr Asn Asp
 1 5 10 15
 Ser Thr Tyr Gln Ser Pro Leu Asn Ser Gln Phe His Gln Ser Pro Phe
 20 25 30
 Leu Gln Thr Gln Ser Pro Asp Tyr Val Ser Leu Arg Glu Glu Glu Asp
 35 40 45
 Asp Asn Asn Asp Lys Asn Leu Asp Ile Met Ser Ser Cys Ile Val Asp
 50 55 60
 Ser Val Ile Tyr Lys Ser Gln Lys Ile Ala Gly Pro Leu Leu Ser Gln
 65 70 75 80
 Ile Ser Asn Leu Asn Ile Gln Gln Ala Leu Ile Ile Arg Glu Leu Leu
 85 90 95
 Phe Thr Leu Leu Gly His Glu Gly His Tyr Ile Gln Tyr Ser Lys Arg
 100 105 110
 Tyr Asp Pro Thr Ser Gln Ile Ser Arg Ile Glu Gly Pro Asp Tyr Lys
 115 120 125
 Ile Ala Lys Asn Leu Asp Ile Ser Leu Lys Val Ile Thr Lys Lys Leu
 130 135 140
 Val Lys Phe Gly Lys Phe Tyr Ser Gly Leu Lys Ser Phe Ile Gln Val
 145 150 155 160
 Phe Asp Asn Asn Lys Phe Gly Lys Ile Val Gln Lys Phe Cys Ser Glu
 165 170 175
 Val Arg Lys Phe Leu Ser Ser Tyr Gln Gln Val Leu Ile Asn Val Glu
 180 185 190
 His Glu Phe Lys Phe Asn Lys Asn Phe Asn Leu Asn Met Leu Asp Ser
 195 200 205
 Leu Leu His Gln Glu Ile Ser Asn Glu Met Thr His Leu Tyr Gln Ile
 210 215 220
 Gly Ile Glu Ile Ser Arg Ile Thr Glu Glu Arg Gln Lys Met Ser Gln
 225 230 235 240
 Ala Glu Ile Met Gly Asn Phe Glu Pro Thr Thr Leu Ala Asn Thr Ser
 245 250 255
 Met Asn Gly Ile Asn Ser Glu Pro Asn Leu Tyr Tyr Gly Lys Phe Asp
 260 265 270
 Cys Cys Lys Gly Gly Leu Leu Leu Gln Val Ile Gln Glu Arg Met Val
 275 280 285
 Tyr Tyr Lys Gly Asp Pro Thr Ser Leu Asp Phe Leu Thr Gln Leu Phe
 290 295 300
 Asp Ile Val Ser Ser Asp Tyr Ile Gly Met Leu Asn Gln Trp Leu Leu
 305 310 315 320
 Glu Gly Val Ile Asn Asp Pro Phe Asp Glu Phe Met Ile Arg Glu Lys
 325 330 335
 Arg Val Pro Asp Ser Phe Met Glu Ile Phe Gln Ser Lys Ser Glu Tyr
 340 345 350
 Tyr Trp Asn Glu Leu Phe Leu Ile Lys Ile Asp Gly Leu Leu Asn Gln
 355 360 365
 Phe Gln Asn Ser Thr Ile Gln Ser Lys Ile Leu Asn Thr Gly Lys Tyr
 370 375 380
 Leu Asn Ile Phe Lys Arg Cys Thr Gly Leu His Asn Phe Glu Ser Leu
 385 390 395 400
 Lys Glu Lys Leu Thr Thr Ile Thr Ser Leu Ala Ala Pro Asp Leu Glu
 405 410 415

Leu Lys Ile Asp Glu Phe Tyr His Arg Ala Asn Lys Met Leu Met Lys
 420 425 430
 Leu Leu Phe Asp Gly Tyr Asn Phe Pro Ser Val Val Asn Ile Phe Gln
 435 440 445
 Arg Leu Phe Leu Phe Ala Asp Ser Phe Gln Ile Asp Asn Phe Ile Asp
 450 455 460
 Ser Thr Phe Ser Glu Leu Lys Arg Gly Lys Leu Lys Ile Ser Val Ser
 465 470 475 480
 Arg Leu Gln Lys Gln Tyr Asp Asp Ile Phe Lys Glu Lys Ile Glu Asn
 485 490 495
 Lys Val Gly Val Arg Pro Ser Val Tyr Asp Val Leu Lys Lys Asn Gln
 500 505 510
 Lys Leu Ser Val Thr Ser Glu Ser Leu Tyr Lys Val Val Glu Glu Leu
 515 520 525
 Met Glu Lys Asn Ser Asp Tyr Leu Ile Ser Asp Asn Asn Leu Arg Gly
 530 535 540
 Ile Phe His Arg Val Ala Ser Leu Arg Asp Asp Ser Arg Leu Thr Ile
 545 550 555 560
 Ser Ser Thr Ala Asp Ser Ala Thr Glu Asn Val Lys Asp Glu Pro Thr
 565 570 575
 Ile Thr Ser Val Asp Leu Thr Ile Pro Leu Pro Phe Pro Leu Asn Leu
 580 585 590
 Val Leu Asn Gln Gln Leu Ser Tyr Gln Tyr Glu Ile Met Phe Lys Leu
 595 600 605
 Leu Ile Asn Ile Lys Phe Ile Ser Lys Tyr Asn Ser Ser Asn Trp Gln
 610 615 620
 Glu Met Asn Tyr Ser Lys Ile Trp Thr Asn Ser His Phe Asn Ser Ser
 625 630 635 640
 Val Lys Lys Trp Ile Leu Arg Cys Arg Val Leu His Ser Arg Ile Cys
 645 650 655
 Ser Phe Ile His Glu Leu Glu Asn Tyr Ile Val His Asp Val Ile Glu
 660 665 670
 His Asn Phe Glu Glu Ile Lys Asn Leu Ile His Thr Thr Ala Thr Asn
 675 680 685
 Leu Ala Thr Ser Glu Leu Gly Ser Asp Ile Asn Asp Glu Gly Asp Asn
 690 695 700
 Ile Phe Asn Gly Ser Leu Ile Arg Gly Thr Phe Asn Asn Asn Ser Ile
 705 710 715 720
 Phe Asp Ser Lys Val His Lys His Arg Thr Thr Thr Tyr Val Glu Gly
 725 730 735
 Ile Ser Thr Val Glu Gln Leu Ile Gln Lys Phe Leu Asp Tyr Ser Ser
 740 745 750
 Thr Leu Leu Asn Asp Ser Leu Leu Thr Arg Glu Glu Ser Leu Arg Gln
 755 760 765
 Leu Arg Lys Met Leu Asp Phe Ile Phe His Phe Asn Asn Tyr Ile Val
 770 775 780
 Gln Val Lys Lys Val Leu Val Leu Leu Asn His Glu Leu Phe Asn Glu
 785 790 795 800
 Tyr Ser Lys Glu Phe Pro Thr Lys Phe Glu Lys Pro Met Asp Gln Glu
 805 810 815
 Ser Ile Asp Lys Arg Phe Ala Asn Leu Ser Asp Thr Phe Leu Met Gln
 820 825 830
 Tyr Glu Lys Phe Gly Glu Asn Leu Val Thr Phe Leu Ala Thr Ile Lys
 835 840 845
 Gln Val Gly Glu Arg Glu Asn Gln Gly Leu Leu Glu Leu Ser Asn Arg
 850 855 860
 Leu Glu Leu Cys Phe Pro Glu
 865 870

<210> 82
 <211> 636
 <212> PRT
 <213> Candida albicans

<400> 82
 Met Ser Gly Pro Ile Ile Cys Ser Lys Phe Asp Gln Ser Gly Asn Tyr
 1 5 10 15
 Leu Ala Thr Gly Met Val Ala Leu Asp Ser His Gln Val Lys Val Gln
 20 25 30
 Ser Ile Thr Ser Ser Gln Ala Ser Leu Asn Thr Ser Phe Thr Leu Glu
 35 40 45
 Lys Ser Asn Lys Leu Val Asn Leu Ala Trp Ile Pro Ser Asp Ser Ile
 50 55 60
 Gln Leu Leu Ala Leu Cys Leu Ser Lys Gly Ser Ile Leu Ile Tyr Ser
 65 70 75 80
 Pro Gln Thr Asn Glu Ile Val Ser Glu Leu Ile Ser Ser Ala Asn Val
 85 90 95
 Ser Ile Leu Asp Phe His Tyr Ser Thr Thr Thr Arg Thr Gly Trp Ser
 100 105 110
 Cys Asp Ile Glu Gly Asn Val Tyr Glu Trp Asp Leu Asn Ser Tyr Leu
 115 120 125
 Leu Val Asp Ser Phe Lys Val Asn Glu Tyr Ile Glu Ser Val Asp Ser
 130 135 140
 Ile Asn Arg Ile Ser Thr Val Met Phe Asn Ser Gln Pro His Leu Leu
 145 150 155 160
 Leu Gly Ser Asn Ala Val Tyr Leu Phe Asn Ile Lys Gln Arg Glu Leu
 165 170 175
 Val Lys Thr Phe Pro Gly His Ile Gln Pro Val Asn Ser Ile Thr Ala
 180 185 190
 Leu Asn Asn Asp Met Phe Leu Thr Ser Ala Lys Gly Asp Arg Phe Val
 195 200 205
 Asn Leu Tyr Gln Leu Asp Lys Thr Ala Thr Lys Ala Val Phe Val Gly
 210 215 220
 Ser Ser Ser Val Ser Ser Leu Ser Val Ser Ile Lys Asp Asp Lys Ser
 225 230 235 240
 Val Leu Val Ile Ile Asn Glu Glu Gly Asp Ile Glu Ile Phe Asn Asn
 245 250 255
 Pro Leu Ala Asp Ala Lys Ser Gln Val Ser Thr Pro Val Pro Lys Lys
 260 265 270
 Lys Arg Lys Gln Val Gly Val Ser Ser Arg Ser Phe Asn Ala Ser Ile
 275 280 285
 Lys Leu Ser Arg Pro Glu Pro Glu Ile Lys Ser Pro Gln Asp Thr His
 290 295 300
 Leu Phe Ile Asn Ala Val Ser Thr Glu Asp Asn Leu Ile Thr Phe Thr
 305 310 315 320
 Trp Leu Glu Asn Ser Thr Ile Pro Phe Phe Asp Thr Leu Lys Trp Ile
 325 330 335
 Asp Glu Thr Gly Ser Leu Leu Leu Glu Ser Ala Lys Val Leu Leu Lys
 340 345 350
 Ser Lys Pro Asn Leu Lys Val Thr Gln His Leu Thr Asn Gly His Asp
 355 360 365
 Val Ala Ala Pro Lys Leu Tyr Thr Glu Gly His Thr Ile Val Ser Asp
 370 375 380
 Gly Ser Asn Ile Arg Asp Leu Glu Phe Gln Asp His Gln Glu Asp Glu
 385 390 395 400
 Glu Asp Thr Glu Glu Ser Leu Ala Glu Lys Leu Glu Arg Leu Ala Met
 405 410 415

Asp Gln Thr Ser Gln Gln Lys Ser Arg Arg Arg Lys Leu Glu Glu Ala
 420 425 430
 Arg Ser Gly Val Ser Leu Ser Ile Val Leu Thr Gln Ser Leu Lys Asn
 435 440 445
 Asn Asp Gln Ala Leu Leu Glu Thr Val Leu Ser Asn Arg Asp Pro Ile
 450 455 460
 Thr Ile Gln Asn Thr Ile Ser Arg Leu Asp Pro Tyr Ser Cys Val Thr
 465 470 475 480
 Phe Leu Asp Lys Leu Ser Glu Lys Ile Gln Arg Gln Pro Thr Arg Phe
 485 490 495
 Asp Gln Val Ser Phe Trp Leu Lys Trp Ile Leu Val Ile His Gly Pro
 500 505 510
 Thr Met Ala Ser Leu Pro Asn Leu Ser Ile Lys Leu Ser Ser Leu Arg
 515 520 525
 Ala Val Leu Asn Lys Lys Ala Glu Glu Leu Pro Arg Leu Leu Glu Leu
 530 535 540
 Gln Gly Arg Leu Lys Leu Met Asp Asp Ser Ala Ala Leu Arg Asn Glu
 545 550 555 560
 Phe Ser Ala Glu Glu Ile Ala Glu Asp Leu Glu Glu Arg Ser Asp Ile
 565 570 575
 Glu Tyr Asn Glu Glu Ile Asp Asp Ala Lys Tyr Val Gly Val Ile Ser
 580 585 590
 Asp Asp Glu Ser Met Asp Asp Val Asp Asp Phe Asp Asp Leu Asp Asp
 595 600 605
 Glu Glu Glu Glu Glu Glu Glu Glu Asp Gly Ile Pro Asp Ala
 610 615 620
 Ala Asn Leu Asp Asp Arg Glu Asp Ser Asp Leu Glu
 625 630 635

<210> 83

<211> 327

<212> PRT

<213> Candida albicans

<400> 83

Met Met Ser Thr Asn Phe Gln Trp Pro Gly Thr Asn Lys Asn Asp Asn
 1 5 10 15
 Thr Glu Val Ser Val Glu Thr Pro Ser Thr Asp Pro His Val Pro
 20 25 30
 Arg Tyr Pro Phe Thr Ala Met Ser His Ala Thr Ala Ser Thr Thr Met
 35 40 45
 Lys Lys Arg Lys Arg Asp Asp Phe Asp Gly Asp Lys Ser Thr Thr Ile
 50 55 60
 Thr Met Asn Thr Thr Thr Arg Lys Tyr Ile Gln Ser Ser Leu Gly
 65 70 75 80
 Ser Ser Lys Phe Lys Lys Ala Lys Thr Pro Lys Ile Ser Gly Gln Pro
 85 90 95
 Leu Pro Leu Pro Arg Leu Ile Glu Ser Leu Asp Lys Ser Asn Leu Gln
 100 105 110
 Lys Leu Val Gln Asp Leu Ile Thr Val His Pro Glu Leu Gln Ser Thr
 115 120 125
 Leu Ile Lys Ile Ser Pro Arg Pro Ser Ile Gln Asp Ser Ile Gln Leu
 130 135 140
 Leu Gln Asp Lys Phe Asp Met Ile Ile Ser His Leu Pro Tyr Lys Cys
 145 150 155 160
 Asp Val Glu Ser Asp Tyr Ser Tyr Leu Arg Ile Lys Pro His Leu Gln
 165 170 175

Glu Phe Leu Ser Ser Val Ser Asp Phe Ile Leu Asn Tyr Leu Pro Pro
 180 185 190
 Leu Glu Thr Asn Met Thr His Ser Leu Gln Phe Leu His Glu Thr Thr
 195 200 205
 Lys Leu Val Tyr Asn Leu Pro Asn Phe Thr Asn Gln Glu Phe Gln Tyr
 210 215 220
 Thr Lys Ser Ser Ala Leu Glu Gln Ile Ala Asn Cys Trp Leu Ile Val
 225 230 235 240
 Leu Ser Gln Asp Glu Glu Lys Glu Gly Asn Thr Asp Val Val Lys Val
 245 250 255
 Ile Gln Glu Leu Glu Leu Leu Glu Lys Leu His Glu His Asn Glu Ile
 260 265 270
 Ser Phe Asn Lys Phe Glu Lys Val Val Asp Tyr Cys Lys Asp Lys Leu
 275 280 285
 Glu Gln His Glu Leu Ile Met Asn Asn Asn Glu Ala Gly Ser Gly Val
 290 295 300
 Thr Ser Ser Ile Ser Asp Leu Ile Thr Val Asp Tyr Ser Lys Tyr Ser
 305 310 315 320
 Ile Ala Asn Thr Thr Ser Ile
 325

<210> 84
 <211> 552
 <212> PRT
 <213> Candida albicans

<400> 84
 Met Pro Thr Asn Ile Gln Gly Glu Glu Val Ile Ile Pro Pro Lys Asp
 1 5 10 15
 Glu Glu Glu Ile Leu Leu Glu Lys Leu Val Phe Gly Asp Ala Ala Gly
 20 25 30
 Phe Glu Asn Asn Leu Lys Lys Leu Asp Asn Leu Tyr Asp Tyr Ser Asp
 35 40 45
 Glu Glu Glu Glu Ile Asp Glu Lys Gly Ser Glu Lys Glu Ser Asp Ile
 50 55 60
 Glu Asp Leu Gln Asp Glu Asp Leu Phe Phe Ile Asp Asp Gly Asn Asn
 65 70 75 80
 Glu Glu His Ser Ser Gly Asp Asp Met Glu Ile Asp Gln Ser Glu Asp
 85 90 95
 Glu Glu Glu Gly Glu Asp Gln Asp Ser Asp Asn Ala Trp Glu Asp Ser
 100 105 110
 Asp Asp Glu Lys Val Asn Ile Ser Leu Leu Thr Ser Asp Lys Leu Lys
 115 120 125
 Lys Leu Arg Lys Thr Pro Gln Asp Ser Val Ile Ser Gly Lys Ser Tyr
 130 135 140
 Ile Ile Arg Leu Arg Ser Gln Phe Glu Lys Ile Tyr Pro Arg Pro Gln
 145 150 155 160
 Trp Ile Glu Asp Ile Glu Asn Asn Ser Asp Asp Glu Lys Asp Leu Ser
 165 170 175
 Asp Glu Asp Lys Val Asp Asp Glu Glu Gly Gln Val Gly Ser Thr Thr
 180 185 190
 Ala Leu Leu Asn Ile Leu Ser Ser Thr Glu Lys Phe Ile Asn Thr Lys
 195 200 205
 Gln Leu Lys Leu Ile Ala Ala Asn Lys Ile Ser Ile Thr Arg Leu Lys
 210 215 220
 Asp Ala Asn Tyr Lys Arg Ile Gly Lys Ser Gly Ile Gln Thr Ile Asp
 225 230 235 240

Phe His Pro Asn Tyr Pro Ile Leu Leu Thr Gly Gly Phe Asp Lys Thr
 245 250 255
 Ile Arg Ile Tyr Gln Ile Asp Gly Lys Ser Asn Asn Phe Ile Thr Ser
 260 265 270
 Tyr Phe Leu Lys Asn Cys Pro Ile Met Glu Ala Ser Phe Tyr Pro Gln
 275 280 285
 Leu Ser Gly Asp Asp Thr Lys Thr Ser Asn Leu Ile Tyr Ala Ser Gly
 290 295 300
 Arg Arg Arg Tyr Met Asn Lys Ile Asn Leu Ser Thr Gly Glu Ile Glu
 305 310 315 320
 Lys Ile Ser Arg Leu Tyr Gly His Glu Gln Thr Gln Lys Ser Phe Glu
 325 330 335
 Tyr Phe Lys Ile Ser Pro Gln Gly Lys Tyr Ile Gly Leu Thr Gly Asn
 340 345 350
 Asn Gly Trp Cys Asn Leu Leu Asn Ala Gln Thr Gly His Trp Val His
 355 360 365
 Gly Phe Lys Ile Glu Gly Thr Ile Val Asp Phe Ala Phe Ala Asn Asp
 370 375 380
 Glu Ser Phe Ile Met Ile Val Asn Ser Ala Gly Glu Val Trp Glu Phe
 385 390 395 400
 Ala Leu Glu Gly Lys Ile Thr Ser Lys Thr Pro Asn Lys Ile Ile Arg
 405 410 415
 Arg Trp Tyr Asp Asp Gly Gly Val Gly Ile Thr Lys Leu Gln Ile Gly
 420 425 430
 Gly Lys Asn Asn Arg Trp Val Ala Ile Gly Asn Asn Asn Gly Ile Val
 435 440 445
 Asn Ile Tyr Asp Arg Ser Val Phe Ala Pro Glu Thr Thr His Pro Lys
 450 455 460
 Pro Ile Lys Thr Val Glu Asn Leu Ile Thr Ser Ile Ser Ser Leu Val
 465 470 475 480
 Phe Asn Pro Asp Gly Gln Leu Leu Cys Ile Ala Ser Arg Ala Lys Arg
 485 490 495
 Asp Ala Leu Arg Leu Val His Leu Pro Ser Gly Ser Val Tyr Ser Asn
 500 505 510
 Trp Pro Thr Ser Gly Thr Pro Leu Gly Lys Val Thr Ser Ile Ala Phe
 515 520 525
 Ser Pro Asn Asn Glu Met Leu Ala Ile Gly Asn Gln Thr Gly Lys Val
 530 535 540
 Thr Leu Trp Arg Leu Asn His Tyr
 545 550

<210> 85
 <211> 715
 <212> PRT
 <213> Candida albicans

<400> 85
 Met Ser Leu Lys Pro Phe Thr Gly Leu Leu Phe Cys Cys Thr Gly Leu
 1 5 10 15
 Glu Ser Thr Thr Arg Arg Glu Val Val Glu Lys Ile Glu Thr Leu Gly
 20 25 30
 Gly Ile His Tyr Ser Asp Leu Met Thr Asp Val Asn Tyr Leu Ile Val
 35 40 45
 Gly Asp Arg Asp Thr Glu Lys Tyr Arg Phe Cys Ile Lys Tyr Arg Pro
 50 55 60
 Asp Ile Ile Phe Ile Asp Ala Asp Ser Ile Phe Thr Ile His Lys His
 65 70 75 80

Trp Ile Asn Gly Glu Asp Glu Asn Ser Asp Leu Leu Arg Ile Glu Lys
 85 90 95
 Tyr Arg Leu Ala Ile Phe Ala Gln Leu Asn Ala Cys Phe Ser Arg Ile
 100 105 110
 Glu Met Ser Thr Ser Gln Ile Asp His Leu Val Asn Thr Val Lys Phe
 115 120 125
 Arg Gln Arg Thr Asn Thr Ser Pro Glu Tyr Phe Arg Pro Lys Asn Leu
 130 135 140
 Phe Lys Leu Phe Val Asp Asn Gly Gly Ile Ala Lys Glu Ser Leu Ser
 145 150 155 160
 Cys His Gln Asn Phe Ile Ile Thr Ala Asp Pro Arg Gly Thr Arg Tyr
 165 170 175
 Asn Lys Ala Leu Glu Trp Asn Val Pro Ala Ile His Pro Ile Trp Ile
 180 185 190
 Val Asp Ser Val Leu Arg Gly Ala Ala Leu Asp Trp Lys Asp Tyr Ile
 195 200 205
 Leu Asn Asn Asn Pro Asn Asp Cys Tyr Asp Arg Gly Cys Asp Val Trp
 210 215 220
 Pro Glu Val Phe Asp Cys Gln Glu Lys Gln Lys Gln Lys Ser Gln Gln
 225 230 235 240
 Gln Pro Lys Arg Leu Glu Ser Thr Glu Pro Glu Val Lys Arg Lys Ile
 245 250 255
 Thr Asn Asn Lys Thr Asn Ala Asp Ile Trp Asn Ser Ile Met Asp His
 260 265 270
 Thr Lys Lys Gln Thr Lys Gln Leu Ile His Asp Lys Thr Trp Asp Asp
 275 280 285
 Asp Glu Glu Glu Glu Asp Asn Asp Asp Asp Gly Asp Thr Gln Thr Lys
 290 295 300
 Asn Glu Lys Asn Asn Gln Tyr Lys Asn Ile Thr Thr Ile Pro Lys Asp
 305 310 315 320
 Gly Lys Gln Lys Pro Glu Leu Asn Gly Lys Ile His Asn Leu Asp Leu
 325 330 335
 Lys Leu Val Ser Glu Ser Lys Glu Asn Ser Pro Asn Val Ser Glu Ser
 340 345 350
 Gln Leu Phe Leu Gly Phe Asn Tyr Tyr Thr Val Gly Phe Asp Ser Arg
 355 360 365
 Glu Phe Asp Leu Leu Ser Lys Ala Ile Glu Asn Tyr Ser Gly Glu Ile
 370 375 380
 Ser Asn Asp Pro Asn Asp Asp Ser Ile Thr His Val Val Ile Pro Ala
 385 390 395 400
 Lys Lys Gly Tyr Gln Ser Met Ser Val Leu Lys Val Leu Pro Ala Asp
 405 410 415
 Leu Lys Ser Arg Ile Ala Asn Gly Phe Val Lys Ile Val Thr Glu Phe
 420 425 430
 Phe Ile Glu Arg Cys Met Phe Tyr Lys Lys Ile Ile Leu Asp Arg Trp
 435 440 445
 Gly Gln Pro Met Lys Gly Leu Val Pro Ser Lys Lys Ser Phe Lys Ile
 450 455 460
 Cys Thr Thr Gly Phe Thr Gly Ile Glu Leu Leu His Ile Glu Lys Leu
 465 470 475 480
 Ile Arg Ser Phe Asn Phe Glu Tyr Cys Glu Thr Leu Ser Glu Gln Arg
 485 490 495
 Asp Leu Leu Ile Leu Asn Val Asn Leu Phe Lys Lys Ser Leu Met Asn
 500 505 510
 Ser Pro Lys Leu Phe Gln Tyr Lys Cys Lys Asp Ile Ile Asn Cys Pro
 515 520 525
 Thr Gly Gly Ser Val Ser Leu Met Ser Ser Lys His Lys Val Glu Ala
 530 535 540

Ala Lys Arg Trp Asn Ile Pro Val Val Ser Val Ala Tyr Leu Trp Glu
 545 550 555 560
 Ile Leu Glu Leu Ser Thr Asn Lys Ser His Ile Ile Met Pro Asp Ile
 565 570 575
 Thr Asp Leu Gln Trp Cys Val Phe Ala Pro Ser Asn Tyr Asn Lys Pro
 580 585 590
 Lys Ser Leu Leu Glu Tyr Val Lys Asn Leu Asp Lys Ala Ser Arg Glu
 595 600 605
 Ser Ser Phe Ser Pro Lys Ser Gln Glu Asn Glu Ala Leu Glu Glu Pro
 610 615 620
 Thr Met Asp Asn Ser Val Arg Leu Pro Ser Pro Arg Arg Val Asn Ser
 625 630 635 640
 Lys Gln Lys Tyr Gly Lys Leu Val Gly Gly Lys Ser Pro Lys Ser Ile
 645 650 655
 Lys Arg Lys Leu Leu Glu Ala Ala Asn Ser Phe Ala Asp Gly Gln Asn
 660 665 670
 Asp His Ser Ile Asn Pro Asp Val Thr Ile Glu Glu Asp Ser Met Ser
 675 680 685
 Gln Ile Arg Tyr Gln Asp Asn Glu Ser Met Ile Asn Gln Glu Arg Leu
 690 695 700
 Leu Glu Lys Leu Asp Gly Ser Ala Val Leu Val
 705 710 715

<210> 86

<211> 1120

<212> PRT

<213> Candida albicans

<400> 86

Met Gly Lys Asp Leu Leu Thr Ala Glu Ala Val Thr Lys Leu Leu Arg
 1 5 10 15
 Ser Lys Asp Thr Ser Ile Thr Glu Ile Val Asn Thr Ala Asn Ser Leu
 20 25 30
 Leu Asn Asn Thr Leu Asp Ile Tyr Leu Pro Gly Lys Glu Val Phe Val
 35 40 45
 Leu Asn Leu Leu Cys Asp Arg Leu Asn Asp Lys Ser Asn Gly Lys Phe
 50 55 60
 Gly Lys Trp Lys Phe Asn Lys Asp Val Trp Asn Leu Leu Ser Val
 65 70 75 80
 Trp Ser Lys Leu Asn His Gln Lys Val Asp Arg Gln Arg Val Ile Gln
 85 90 95
 Arg Leu Lys Ile Ile Glu Ile Ile Ile Leu Val Leu Gln Gln Asn Asn
 100 105 110
 Asp Asn Glu Val Phe Ser Ser Leu Phe Glu Phe Leu Gly Ile Met Phe
 115 120 125
 Gln Glu Ser Tyr Ile Ile Ala Asp Glu Asn Ser Ala Thr Gln Leu Leu
 130 135 140
 Lys Cys Phe Val Glu His Met Asp Val Leu Gln Ala Ser Asp Ser Ile
 145 150 155 160
 Val Ser Trp Thr Glu Leu Val Arg Asp Ile Tyr Thr Arg Ala Cys Ser
 165 170 175
 Lys Ile Ser Leu Glu Gly Ser Lys Lys Phe Tyr Asn Lys Phe Phe Glu
 180 185 190
 Asp Cys Cys Phe Pro Leu Ile Glu Tyr Leu Ala Ile Ser Glu Gly Ser
 195 200 205
 Ser Val Ser Pro Ile Leu Lys Glu Leu Leu Ile Gln Gly Val Phe Asn
 210 215 220

Ala Asp Ser Thr Lys Tyr Tyr Gln Ser Ser Leu Glu Arg Glu Leu Lys
 225 230 235 240
 Lys Lys Asp Ile Lys Glu Val Ser Val Ile Tyr Leu Tyr Thr Leu Thr
 245 250 255
 Val Gln Leu Phe Ser Ala Lys His Met Glu Ile Cys Glu Gly Val Tyr
 260 265 270
 Ser Ile Met Ala Ser Lys Cys Pro Asp Leu Ala Glu Lys Leu Leu Ser
 275 280 285
 Ile Leu Ala Ser Cys Arg Lys Thr Ile Ser Lys Pro Phe Ile Glu Ser
 290 295 300
 Ile Tyr Lys Val Glu Val Ala Asp Lys Pro Phe Lys Gln Leu Asn Trp
 305 310 315 320
 Asp Met Val Lys His Ile Phe Ala Ile Asp Ser Glu Leu Ala Ile Ser
 325 330 335
 Lys Ser Gly Phe Leu Phe Lys Thr Tyr Lys Ser Glu Phe Gln Leu Asp
 340 345 350
 Asp Lys Val Val Pro Val Ala Glu Val Ile Val Asp Gly Phe Ala Arg
 355 360 365
 Asn Arg Glu Leu Ser Asp Phe Phe Thr Lys Val Trp Pro Lys Ala Ile
 370 375 380
 Lys Arg Asp Glu Ile Trp Glu Ser Asp Glu Phe Ile His Thr Val Ser
 385 390 395 400
 Gln His Val Lys Thr Phe Ser Gly Lys Gln Leu Ile Asp Val Ile Glu
 405 410 415
 Ser Ser Phe Tyr Ala Asp Lys Gly Ser Gln Arg Ala Ile Phe Thr Ala
 420 425 430
 Ile Thr Lys Gly Leu Thr Ser Ser Ala Asn Leu Ile Asp Ala Val
 435 440 445
 Lys Gln Thr Leu Leu Asp Arg Ser Asn Tyr Phe Asn Ala Thr Glu Asn
 450 455 460
 Phe Trp Cys Ile Arg Tyr Tyr Leu Leu Cys Leu Tyr Gly Thr Asp Phe
 465 470 475 480
 Thr Ile Ala Glu Gln Asn Met Lys Gln Asn Ile Asp Leu Tyr Tyr His
 485 490 495
 Phe Ser Ile Phe Arg Leu Leu Glu Leu Gln Val Ile Lys Glu Tyr Ser
 500 505 510
 Lys Ser Asp Gln Lys Tyr Phe Ile Ala Cys Ile Glu Gly Glu Lys Glu
 515 520 525
 Met Ile Ser Pro Ile Phe Lys Arg Trp Leu Val Ile Phe Asn Lys Phe
 530 535 540
 Phe Asp Ser Asp Leu Leu Ile Lys Leu Ile Ser Leu Gly Tyr Pro Asp
 545 550 555 560
 Ile Glu Phe Asp Asp Val Phe Phe Glu Gln Pro Lys Leu Thr Thr Ser
 565 570 575
 Leu Ile Arg Phe Ile Thr Glu Asn Leu Pro Ala Arg Met Asp Leu Ile
 580 585 590
 Ala Ser Ile Pro Ile Val Cys Phe Asn Lys Ala Phe Lys Lys Glu Leu
 595 600 605
 Leu Asn Gly Leu Phe Val Leu Phe Val Ser Asn Pro Thr Lys Glu Thr
 610 615 620
 Leu Glu Asn Ile Gln Tyr Leu Leu Gly Gln Pro Thr Tyr Ser Ser Ile
 625 630 635 640
 Leu Glu Thr Asn Phe Asp Asn Met Leu Lys Leu Leu Thr Val Ser Thr
 645 650 655
 Glu Glu Ser Lys Leu Ile Ala Tyr Asn Val Ile Glu Ile Val Trp Lys
 660 665 670
 Asn Asn Val Arg Gln Ile Lys Asn Glu Glu Asn Gln Lys Tyr Val Asn
 675 680 685

Asp Ala Ile Ser Lys Leu Ser Ser Tyr Leu Asp Ser Met Ser Gln Gln
 690 695 700
 Ile Ile Ser Pro Glu Leu Glu Ala Ile Ser Ile Ile Leu Thr Asn Thr
 705 710 715 720
 Lys Glu Val Gly Leu Phe Glu Asn Thr Glu Lys Gly Leu Asn Lys Leu
 725 730 735
 Asn Glu Lys Phe Thr Asn Tyr Cys Ile Asn Thr Leu Asn Asn Cys Asn
 740 745 750
 Thr Gln Asn Phe Ile Thr Val Arg Trp Leu Leu Gln Ala Leu Val Met
 755 760 765
 Leu Pro Pro Lys Ser Leu Ser Phe Glu Asn Val Ile Ser Cys Thr Lys
 770 775 780
 Arg Leu Asp Pro Asn Ile Leu Lys Asp Asn Ser Ile Gln Ser Thr Leu
 785 790 795 800
 Phe Gln Leu Ile Cys Lys Thr Ile Asp Phe Asn Tyr Lys Ser Leu Val
 805 810 815
 Tyr Val Leu Ser Leu Phe Val Ser Leu Ser Ser Gly Arg Asn Thr Glu
 820 825 830
 Leu Tyr Thr Val Leu Lys Ser Leu Phe Gln Lys Phe Ser Lys His Ser
 835 840 845
 Gln Leu Tyr Phe Glu Val Phe Asp Phe Phe Thr Arg Ser Ile Asp Ala
 850 855 860
 Val Pro Val Glu Phe Asn Leu Ser Phe Ala Gln Ile Ala Ser Ile Phe
 865 870 875 880
 Leu Ser Thr Val Pro Lys Asp Ala Asp Ala Asn Arg Tyr Asn Ser Lys
 885 890 895
 Cys Phe Thr Phe Tyr Val Asn Ala Leu Gln Ser Gly Asn Glu Cys Val
 900 905 910
 Ala Met Gln Ile Leu Thr Ser Leu Lys Asp Leu Leu Thr Asn Gln Ser
 915 920 925
 Trp Ile Phe Lys Gln Asn Leu Leu Glu Ile Thr Leu Val Ile Val Lys
 930 935 940
 Thr Gly Leu Gln Lys Leu Asn Ser Phe Ala Asn Gln Glu Gln Ile Tyr
 945 950 955 960
 Ile Leu Ser Thr Gln Ile Val Ser His Ile Leu Leu Tyr His Arg Phe
 965 970 975
 Lys Ile Ala Thr Arg His His Leu Val Leu Asn Val Met Ser Ser Leu
 980 985 990
 Leu Lys Tyr Leu Ala Asp Gly Thr Ser Lys Leu Ser Ser Asn Thr Glu
 995 1000 1005
 Ala Ala Ser Ala Tyr Ala Arg Leu Leu Ser Asn Leu Cys Glu Pro Ser
 1010 1015 1020
 Glu Arg Val Gly Asp Lys Met Phe His Leu Thr Thr Ser Ala Ser Tyr
 1025 1030 1035 1040
 Phe Lys Lys Leu Leu Arg Lys His Leu Ser Val Leu Leu Ser Asn Tyr
 1045 1050 1055
 Ile Tyr Phe Asn Leu Lys Tyr Thr Phe Thr Arg Thr Val Asn Asp Ala
 1060 1065 1070
 Ile Met Pro Gly Ile Tyr Ser Met Phe Thr Val Leu Ser Gln Asn Glu
 1075 1080 1085
 Leu Arg Val Val Asn Asp Ser Leu Asp Tyr Gly Gly Lys Ala Phe Tyr
 1090 1095 1100
 Lys Thr Leu Tyr Asn Asp Tyr Lys Asp His Gly Lys Trp Lys Asp Gln
 1105 1110 1115 1120

<210> 87
 <211> 196
 <212> PRT

<213> Candida albicans

<400> 87

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Met Ser Ala Asp Glu Asn Asn Lys Val Arg Phe Glu Arg Leu Arg Leu
 1           5           10           15
Val Ala Arg Lys Ala Leu Glu Gln Ser Ile Lys Lys Ser Leu Thr Met
      20           25           30
Glu Gln Val Lys Thr Cys Phe Pro Thr Leu Val Thr Ser Gln Asp Gly
      35           40           45
Val Arg Ser Leu Glu Leu Ala Leu Ser Gln Met Ser Gly Phe Trp His
      50           55           60
Ala Asn Ser Leu Asp Glu Phe Asp Leu Ile Tyr Lys Glu Lys Asp Ile
      65           70           75           80
Glu Ser Lys Leu Asp Glu Leu Asp Asp Ile Ile Gln Asn Ala Gln Arg
      85           90           95
Thr Lys Asp Ser Gly Lys Glu Pro Ser Asn Ile Asp Gln Leu Ser Pro
      100          105          110
Leu Glu Ile Val Asp Ser Thr Ile Val Ser Asn Ser Lys Asn Val Leu
      115          120          125
Asp Ser Leu Gln Met Ile Tyr Asp Gln Leu Cys Leu Asp Asn Ala Glu
      130          135          140
Leu Tyr Thr Glu Leu Ser Glu Leu Thr Lys Glu Ser Thr Arg Ile Asn
      145          150          155          160
Asn Ser Ile Lys Ser Gly Ile Glu Gln Leu Asn Lys Glu Ala Asn Ser
      165          170          175
Val Glu Leu Glu Lys Ala Gly Leu Gln Ile Asp Lys Leu Ile Asp Ile
      180          185          190
Leu Glu Glu Lys
      195

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<210> 88

<211> 471

<212> PRT

<213> Candida albicans

<400> 88

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Met Ala Ser Ser Ile Leu Arg Ser Lys Ile Ile Gln Lys Pro Tyr Gln
 1           5           10           15
Leu Phe His Tyr Tyr Phe Leu Ser Glu Lys Ala Pro Gly Ser Thr Val
      20           25           30
Ser Asp Leu Asn Phe Asp Thr Asn Ile Gln Thr Ser Leu Arg Lys Leu
      35           40           45
Lys His His His Trp Thr Val Gly Glu Ile Phe His Tyr Gly Phe Leu
      50           55           60
Val Ser Ile Leu Phe Phe Val Phe Val Val Phe Pro Ala Ser Phe Phe
      65           70           75           80
Ile Lys Leu Pro Ile Ile Leu Ala Phe Ala Thr Cys Phe Leu Ile Pro
      85           90           95
Leu Thr Ser Gln Phe Phe Leu Pro Ala Leu Pro Val Phe Thr Trp Leu
      100          105          110
Ala Leu Tyr Phe Thr Cys Ala Lys Ile Pro Gln Glu Trp Lys Pro Ala
      115          120          125
Ile Thr Val Lys Val Leu Pro Ala Met Glu Thr Ile Leu Tyr Gly Asp
      130          135          140
Asn Leu Ser Asn Val Leu Ala Thr Ile Thr Thr Gly Val Leu Asp Ile
      145          150          155          160
Leu Ala Trp Leu Pro Tyr Gly Ile Ile His Phe Ser Phe Pro Phe Val
      165          170          175

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Leu Ala Ala Ile Ile Phe Leu Phe Gly Pro Pro Thr Ala Leu Arg Ser
 180 185 190
 Phe Gly Phe Ala Phe Gly Tyr Met Asn Leu Leu Gly Val Leu Ile Gln
 195 200 205
 Met Ala Phe Pro Ala Ala Pro Pro Trp Tyr Lys Asn Leu His Gly Leu
 210 215 220
 Glu Pro Ala Asn Tyr Ser Met His Gly Ser Pro Gly Gly Leu Gly Arg
 225 230 235 240
 Ile Asp Lys Leu Leu Gly Val Asp Met Tyr Thr Thr Gly Phe Ser Asn
 245 250 255
 Ser Ser Ile Ile Phe Gly Ala Phe Pro Ser Leu His Ser Gly Cys Cys
 260 265 270
 Ile Met Glu Val Leu Phe Leu Cys Trp Leu Phe Pro Arg Phe Lys Phe
 275 280 285
 Val Trp Val Thr Tyr Ala Ser Trp Leu Trp Trp Ser Thr Met Tyr Leu
 290 295 300
 Thr His His Tyr Phe Val Asp Leu Ile Gly Gly Ala Met Leu Ser Leu
 305 310 315 320
 Thr Val Phe Glu Phe Thr Lys Tyr Lys Tyr Leu Pro Lys Asn Lys Glu
 325 330 335
 Gly Leu Phe Cys Arg Trp Ser Tyr Thr Glu Ile Glu Lys Ile Asp Ile
 340 345 350
 Gln Glu Ile Asp Pro Leu Ser Tyr Asn Tyr Ile Pro Ile Asn Ser Asn
 355 360 365
 Asp Asn Glu Ser Arg Leu Tyr Thr Arg Val Tyr Gln Glu Ser Gln Val
 370 375 380
 Ser Pro Pro Ser Arg Ala Glu Thr Pro Glu Ala Phe Glu Met Ser Asn
 385 390 395 400
 Phe Ser Arg Ser Arg Gln Ser Ser Lys Thr Gln Val Pro Leu Ser Asn
 405 410 415
 Leu Thr Asn Asn Asp Gln Val Pro Gly Ile Asn Glu Glu Asp Glu Glu
 420 425 430
 Glu Glu Gly Asp Glu Ile Ser Ser Ser Thr Pro Ser Val Phe Glu Asp
 435 440 445
 Glu Pro Gln Gly Ser Thr Tyr Ala Ala Ser Ser Ala Thr Ser Val Asp
 450 455 460
 Asp Leu Asp Ser Lys Arg Asn
 465 470

<210> 89

<211> 1179

<212> PRT

<213> Candida albicans

<400> 89

Met Thr Ser Ser Ser Gln Leu Ser Ala Ser Ser Asn Glu Ser Ile Gln
 1 5 10 15
 Asn Glu Arg Leu Leu Ser Ser Ser Leu Phe Asp Gln Ile Arg Pro Val
 20 25 30
 Cys Ile Glu Leu Ser Glu Ala Ser Thr Ser Gln Pro Phe Asn Thr Asn
 35 40 45
 Lys Val Val Asn Leu Met Ile Ser Met Glu Asp Ile Leu Lys Lys His
 50 55 60
 His Asp Glu Tyr Asn Lys Asp Gly Asn Phe Arg Ile Tyr Gln Leu Ser
 65 70 75 80
 Pro Lys Leu Ala Asp Tyr Ile Phe Tyr Pro Leu Ser Asn Ile Leu Lys
 85 90 95

Gln Pro Ala Leu Asp Asp Thr Ile Ile Gln His Leu Phe Gly Ile Ile
 100 105 110
 Arg Phe Leu Val Glu Tyr Ser Trp Ser Phe Asn Val Asn Phe Val Leu
 115 120 125
 Thr Asp Gln Leu Leu Pro Leu Val Ile Tyr Leu Ser Ser Gly Asp Leu
 130 135 140
 Asn Lys Glu Pro Leu Leu Ile Thr Lys Lys Ser Ile Gln Phe Lys Ile
 145 150 155 160
 Ala Thr Val Ser Val Leu Tyr Thr Ile Thr Ser Thr Leu Asn Lys Glu
 165 170 175
 Tyr Phe Gln Ser Leu Thr Glu Lys Arg Leu Leu Phe Ile Ser Asn Val
 180 185 190
 Ile Thr Ile Cys Leu Ser Ile Ile Val Gly Ser Arg Val Glu Ser Gln
 195 200 205
 Asp Thr Ile Gln Leu Val Leu Lys Cys Leu Ser Leu Ile Ser Asn Val
 210 215 220
 Lys Arg Tyr Leu Asn Ser Ser Gln Ile Ser Ile Ile Leu Pro Gly Ile
 225 230 235 240
 Val Ser Ser Ile Thr Lys Phe Ile Ser Leu Asn Leu Asn Leu Asn Tyr
 245 250 255
 Gln Ile Ile Ile Gln Phe Leu Arg Leu Leu Ser Gly Phe Ile Cys Ala
 260 265 270
 Ser Phe Asn Asp Lys Glu Leu Asp Ala Gln Ile Glu Leu Asn Glu Gly
 275 280 285
 Ile Ser Asp Ile Ser Glu Ile His Val Gly Trp Asp Asp Asp Asn Glu
 290 295 300
 Thr Leu Gly Asn Asn Ser Leu Tyr Ser Asp Val Thr Ile Thr Glu Asn
 305 310 315 320
 Asp His Arg Ser Ser Ala Trp Leu Lys Ala Thr Ser Lys Gln Leu Lys
 325 330 335
 Leu Ser Leu Ile Ile Ile Phe Lys Ser Ile Leu Leu Gly Ser Arg Asn
 340 345 350
 Arg His Arg Leu Arg Ser Lys Gln Glu Leu Tyr Asp Glu Ile Leu Gly
 355 360 365
 Phe Val Glu Thr Ile Leu Lys Asn Cys Phe Asn Ser Leu Phe Lys Glu
 370 375 380
 Phe Ala Ser Leu Ala Ile Asp Ile Val Ser Ile Leu Gly Tyr Val Thr
 385 390 395 400
 Ser Glu Asp Asn Lys Glu Met Ala Asp Lys Thr Asn Lys Leu Ser Asn
 405 410 415
 Thr Leu Cys Met Ile Ile Glu Gly Glu Thr Asn Lys Glu Glu Val Leu
 420 425 430
 Phe Glu Leu Val Lys Thr Lys Leu Ala Asp Leu Ile Asp Asn Lys Leu
 435 440 445
 Ser Gly Ile Val Phe Ala Leu Asp Glu Asp Lys Ile Ser Ser Thr Val
 450 455 460
 Ala Ser Met Met Phe Asn Phe Ser Leu Leu Leu Cys Leu Ser Arg Lys
 465 470 475 480
 Val Lys Leu Asp Cys Glu Asp Leu Asp Ser Leu Lys Gln Arg Cys Leu
 485 490 495
 Ala Leu Leu Thr Glu Tyr Val Ala Asp Arg Phe Lys Phe Glu Ser Ser
 500 505 510
 Lys Pro Ile Lys Ser Ser Asn Ala Ser Gly Leu Leu Glu Thr Ser Ser
 515 520 525
 Met Thr Asn Gln Leu Asp Ser Ile Glu Leu Pro Gly Tyr Ile Asn Ala
 530 535 540
 Lys Ser Val Val Lys Gln Glu Pro Leu Lys Lys Glu Gln Asp Lys Arg
 545 550 555 560

Ala	Tyr	Ile	His	Asn	Leu	Lys	Thr	Ile	Ser	Arg	Asn	Trp	Asn	Thr	Asn	
				565					570					575		
Glu	Ile	Asn	Asn	Ser	Ser	Gly	Asn	Thr	Leu	Ile	Gly	Ile	Ser	Ser	Lys	
				580					585					590		
Phe	Ser	Glu	Thr	Ile	Leu	Gln	Asn	Phe	Ile	Asn	Tyr	Leu	Ser	Ser	Leu	
				595					600					605		
Lys	Tyr	Glu	Ala	Ser	Asn	Ser	Ser	Thr	Leu	Thr	Glu	Leu	Glu	Asn	Ile	
				610					615					620		
Phe	Glu	Leu	Ala	Asp	Asp	Asn	Asp	Met	Ile	Thr	Lys	Ser	Thr	Ser	Leu	
				625					630					635		
Trp	Val	Ala	Ser	Asn	Tyr	Tyr	Lys	Arg	Ser	Thr	Leu	Gly	Lys	Val	Ile	
				645					650					655		
Asn	Phe	Asp	Leu	Gly	Lys	Tyr	Leu	Val	Leu	Asp	Asp	Asp	Glu	Asp	Met	
				660					665					670		
Glu	Ile	Asp	Asp	Asp	Thr	Lys	Glu	Met	Ser	Phe	Leu	Val	Leu	Ser	Arg	
				675					680					685		
Ala	Glu	Glu	Leu	Leu	Glu	Glu	Ile	Ser	Glu	Asn	Gln	Glu	Lys	Tyr	Ser	
				690					695					700		
Ser	Gln	Thr	Tyr	Ile	Leu	Ala	Tyr	Asn	Ala	Ala	Leu	Gln	Ser	Ile	Lys	
				705					710					715		
Val	Val	Ala	Gly	Ser	Ile	Pro	Leu	Asp	Gln	Phe	Arg	Thr	Asn	Phe	Leu	
				725					730					735		
Met	Asp	His	Leu	Leu	Ser	Val	Phe	Gln	Ala	Leu	Thr	Tyr	Asn	Asp	Met	
				740					745					750		
Pro	Glu	Ile	Gln	Leu	Gln	Ala	Gln	Ser	Thr	Leu	Lys	Val	Val	Leu	Asp	
				755					760					765		
Thr	Tyr	Tyr	Asn	Gly	Ser	Met	Val	Asn	Leu	Ile	Ser	Asp	Asn	Ser	Asp	
				770					775					780		
Tyr	Leu	Ile	Asp	Ser	Ile	Ser	Leu	Gln	Met	Ser	Val	Ala	Ser	Asn	Leu	
				785					790					795		
Thr	Pro	Met	Leu	Pro	Gly	Ile	Leu	Leu	Ile	Ile	Val	Lys	Ile	Ala	Gly	
				805					810					815		
Ile	Gln	Leu	Leu	Glu	Ser	Asn	Gln	Leu	His	Asp	Val	Leu	Thr	Asp	Met	
				820					825					830		
Phe	Val	Ile	Leu	Asp	Ser	Phe	His	Gly	Tyr	Asn	Lys	Leu	Val	Glu	Ser	
				835					840					845		
Phe	Phe	Ile	Val	Phe	Glu	Ala	Leu	Ile	Asp	Gln	Ile	His	His	Lys	Phe	
				850					855					860		
Asp	Ser	Gln	Leu	Lys	Val	Glu	Phe	Lys	Glu	Ser	Ser	Lys	Thr	Asn	Thr	
				865					870					875		
Ser	Leu	Tyr	Lys	Pro	Trp	Gly	Met	Thr	Asn	Lys	Asp	Gln	Leu	Leu	Glu	
				885					890					895		
Leu	Leu	Asn	Glu	Ser	Asn	Lys	Met	Val	Asp	Lys	Tyr	Glu	Gly	Tyr	Asp	
				900					905					910		
Ser	Asn	Lys	Glu	Tyr	Phe	Lys	Arg	Lys	Ala	Asp	Leu	Pro	Phe	Ser	Glu	
				915					920					925		
Met	Asp	Ala	Asp	Ser	Asp	Asp	Glu	Glu	Glu	Asp	Asp	Glu	Ala	Asn	Ile	
				930					935					940		
Asp	Asp	Asn	Gly	Glu	Glu	Glu	Glu	Glu	Lys	Glu	Ile	Trp	Ser	Ser		
				945					950					955		
Pro	Val	Ser	Lys	Asp	Ile	Tyr	Met	Ile	Ser</							

Val Thr Gly Ser Lys Ser Leu Ser Thr Ser Ile Glu Ser Asn Gly Glu
 1025 1030 1035 1040
 Tyr Ala Ser Glu Asp Ile Gly Val Met Thr Glu Ala Leu Gln Leu Val
 1045 1050 1055
 Thr Glu Ile Leu Glu Glu Asp Lys Arg Arg Tyr Glu His Phe Phe Ser
 1060 1065 1070
 Lys Lys Phe Gln Glu Ala Trp Glu Phe Ile Ser Arg His Ser Lys Leu
 1075 1080 1085
 Val Arg Gln Arg Glu Val Thr Ser Thr Thr Asn Ile Arg Glu Gln Lys
 1090 1095 1100
 Gln Leu Val Val Ser Glu Lys Ala Ile Tyr Thr Phe Arg Asn Tyr Pro
 1105 1110 1115 1120
 Leu Leu Lys Thr Ser Leu Val Thr Phe Leu Ile Thr Gly Val Gln Asn
 1125 1130 1135
 Tyr Glu Lys Met Ile Pro Asp Ile His Arg Phe Glu Ile Ile Lys Leu
 1140 1145 1150
 Cys Tyr Glu Leu Gln Ile Pro Gln Ser Ile Pro Leu Ser Arg Asp Thr
 1155 1160 1165
 Ile Gly Val Leu Glu Val Leu Lys Asn Thr Thr
 1170 1175

<210> 90

<211> 278

<212> PRT

<213> *Candida albicans*

<400> 90

Met Ser Ser Leu Phe Ile Asn Glu Glu Asp Asp Met Thr Pro Glu Pro
 1 5 10 15
 Tyr Lys Pro Ser Thr Ser Thr Ile Arg Glu Glu Glu Glu Val Gln
 20 25 30
 Val Lys Gln Glu Phe Pro Asp Glu Lys Met Val Asp Pro Asp Glu Asp
 35 40 45
 Asp Pro Ile Val Glu Ser Ile Pro Leu Leu Ile Asn Thr Val Pro Glu
 50 55 60
 Arg Ala Lys Gln Ser Leu His Val Leu Gln Tyr Ala Gly Arg Pro Lys
 65 70 75 80
 Ser Arg Pro Asn Arg Ala Gly Asn Cys His Ala Ser Ile Lys Pro Glu
 85 90 95
 Ser Gln Tyr Leu Gln Val Lys Val Pro Leu Asp Thr Glu Lys Phe Phe
 100 105 110
 Asn Val Asp Lys Ile Gln Glu Trp Gly Glu Gln Ile Val Glu Gln Thr
 115 120 125
 Ile Ser Gly Val Leu Asp Gly Ser Tyr Glu Val Gly Asn Tyr Ala Ala
 130 135 140
 Lys Ile Ile Asn Asp Ser Asp Gly Arg Arg Val Val Leu Ile Pro Val
 145 150 155 160
 Asp Ser Thr Val Gln Leu Lys Pro Ser Phe Lys Tyr Ile Asp Asp Leu
 165 170 175
 Glu Ala Gln Ser Ile Gln Gln Arg Arg Gln Gln Glu Ser Thr Asn Glu
 180 185 190
 Lys Pro Ala Asn Val Gln Ile Leu Gln Ser Ala Ala Lys His Ser Thr
 195 200 205
 Gln Ser Gly Glu Phe Ser His Ser Leu Gly Asp Ser Leu Lys Ser Val
 210 215 220
 Lys His Phe Glu Glu Glu Glu Trp Gln Asn Leu Ile Trp Lys Arg Gly
 225 230 235 240

Asp Asp Asp Val Thr Lys Ser Ile Lys Phe Gly Leu Asp His His Thr
 245 250 255
 Asp Thr Asn Ile Glu Leu Lys Thr Asn Thr Ser Tyr Asp Glu Tyr Ile
 260 265 270
 Asp Met Leu Ile Asn Asn
 275

<210> 91
 <211> 492
 <212> PRT
 <213> Candida albicans

<400> 91
 Met Lys Gln His Pro Leu Val Thr Ala Tyr Lys Gly Ile Asp Asp Leu
 1 5 10 15
 Gln Gln Leu Lys Lys Trp Phe Tyr Glu Tyr Asn Asp Thr Ile Asp His
 20 25 30
 Arg Lys Lys Ala Ile Ser Lys Val Lys Gly Leu Leu Thr Arg Gly Lys
 35 40 45
 Leu Pro His Gly Val Glu Ala Thr Ser Leu Leu Thr Ser Ile Val Leu
 50 55 60
 Asp Asp Leu Gln Arg Lys Asp Ile Asp Ser Cys Val Leu Gln Leu Ser
 65 70 75 80
 Tyr Thr Met Ala Leu Ile Arg Phe Val Asn Gly Leu Leu Asp Pro Tyr
 85 90 95
 Gln Gln Ser Asn Tyr Ala Ile Pro Met His Leu Leu Ala Lys Gln Leu
 100 105 110
 Asn Leu Pro Thr Tyr Phe Val Glu Leu Arg His Met Gly Thr His Glu
 115 120 125
 Asn Leu Pro Ser Leu Asp Ile Leu Arg Ser Thr Cys Ser Lys Ala Leu
 130 135 140
 Thr Trp Leu Tyr Asp Asn Tyr Trp Cys His Val Glu Glu Ala Asn Gln
 145 150 155 160
 Asp Lys Gln Val Ser Ile Gly Gly Pro Leu Thr Asp Ala Val Glu Phe
 165 170 175
 Arg Ser Asn Asp Leu Arg Thr Arg Ile Glu Asp Ser Gln Ile Tyr Asn
 180 185 190
 Asn Leu Lys Ala Phe Lys Arg Ile Arg Lys Gln Asp Leu Asn Lys Val
 195 200 205
 Tyr Glu Lys Asn Asp Thr Thr Ser Asp Leu Ala Ala Thr Tyr His Arg
 210 215 220
 Cys Val Ser Asp Ile Val Glu Phe Ala Lys Glu Asn Cys Asp Leu Leu
 225 230 235 240
 Val Asn Val Leu Leu Leu Lys Asn Tyr Leu Ile Tyr Pro Ser Ser Lys
 245 250 255
 Val Lys Asp Lys Lys Ser Lys Phe Asn Pro Leu Ile Ile Lys Leu Tyr
 260 265 270
 Glu Pro Leu Phe Asp Ala Leu Gly Leu Ser Phe Lys Leu Lys Cys Phe
 275 280 285
 Ser Lys Thr Ile Glu Leu Ile Glu Ala Thr Pro Ser Ser Phe Val Asp
 290 295 300
 Lys Lys Val Tyr Arg Lys Leu Gly Phe Thr Glu Lys Phe Glu Tyr Asp
 305 310 315 320
 Glu Leu Phe Gln Val Met Glu Trp Val Leu Tyr Phe Met Gln Asp Leu
 325 330 335
 Leu Arg Asn Glu Asn Val Pro Ser Pro Val His Asn Lys Asn Glu Leu
 340 345 350

Val Ile Leu Phe Leu Asp Ser Leu Lys Ser Ile Glu Gln Lys Ile Ser
 355 360 365
 Gln Ser Leu Leu Pro Ser Phe Ala Lys Ile Leu Gln Gly Leu Cys Asp
 370 375 380
 Val Val Asn Asp Gly Val Lys Ser Glu Ile Asp Pro Glu Thr Val Gln
 385 390 395 400
 Lys Leu Asp Ala Trp Asn Lys Ser Leu Asn Asn Leu His Ser Thr Lys
 405 410 415
 Lys Ile Phe Glu Leu Pro Pro Ser Leu Asp Asp Leu Leu Gly Leu Ser
 420 425 430
 Pro Ser Pro Gly Pro Ile Pro Glu Thr Thr Ser Ser Asn Pro Met Lys
 435 440 445
 His Val Leu Asp Asp Asp Asp Glu Glu Glu Glu Gly Val Arg Arg
 450 455 460
 Lys Gln His His Ser Ser Asp Ser Lys Thr Tyr Ile Leu Lys Pro His
 465 470 475 480
 Lys Asn Trp Arg Pro Val Pro Phe Gly Thr Cys Ile
 485 490

<210> 92

<211> 409

<212> PRT

<213> Candida albicans

<400> 92

Met Thr Ser Ser Ile Asn Ile Leu Leu Leu Leu His Pro Thr Val Val
 1 5 10 15
 Thr Asp Ala Gln Leu Val Glu Gln Ile Lys Ser Lys Ile Tyr Gln Ser
 20 25 30
 His Asn Asn Asn Asn Asn Asn Gly Gly Thr Thr Thr Thr Thr Thr
 35 40 45
 Gly Thr Val Asn Ile Asn Leu Asn Gln Gln Ile Ile Asp Arg Val Thr
 50 55 60
 Lys Gly Ile Ile Glu Leu Pro Tyr Asp Tyr Tyr Asp Glu Ile Ile Tyr
 65 70 75 80
 Ile Asn Pro Asn Asn Glu Ser Gln Tyr Arg Glu Ile Pro Ile Ser Leu
 85 90 95
 Met Gln Leu Ile Tyr Lys Leu Leu Lys Ser Asn Gly Lys Phe Lys Gly
 100 105 110
 Asp Leu Pro Leu Asp Gln Asn Leu Asp Val Leu Met Thr Gly Phe Ile
 115 120 125
 Ile Glu Glu Glu Glu Lys Glu Lys Glu Lys Glu Glu Asn Asn Leu Glu
 130 135 140
 Gly Glu Leu Val Asn Val Trp Val Lys Pro Ile Pro Val Asp Glu Pro
 145 150 155 160
 Val Val Thr Leu Leu Lys Lys Lys Thr Thr Thr Ser Asn Thr Thr Thr
 165 170 175
 Ile Lys Lys Ser Leu Pro Leu Phe Lys Lys Leu Asn Lys Asp Glu Ile
 180 185 190
 Asn Asn Ser Asp Lys Asp Ile Asn Asn Asp Asn Ile Thr Asn Asn Asn
 195 200 205
 Asn Asn Asn Asn Asn Lys Arg Lys Leu Val Glu Thr Lys Leu Thr Tyr
 210 215 220
 Phe Ser Ser Asp Asp Glu Asn Ser Ser Asp Gly Ser Val Leu Glu Asn
 225 230 235 240
 Asp Asp Ile Asp Asp Asp Asp Glu Leu Ile Asp Glu Asn Asp Leu Leu
 245 250 255

Asn Phe Asn Asn Asn Asn Asn Thr Asn Gly Gly Ser Leu Leu Ser Asp
 260 265 270
 Lys Leu Ile Thr Pro Arg Lys Cys Asp Ile Ser Leu Asn Gly Gly Lys
 275 280 285
 Lys Arg Lys Lys Ala Cys Lys Asp Cys Thr Cys Gly Leu Lys Glu Leu
 290 295 300
 Glu Glu Leu Glu Val Ser Asn Gln Gln Asn Leu Gln Asp Gln Ile Leu
 305 310 315 320
 Gly Lys Leu Ala Gln Ser Ala Thr Leu Glu Ala Ile Lys Ile Glu Glu
 325 330 335
 Arg Leu Lys Gln Gln Gln Gln Gln Gln Gln Lys Val Lys Val Lys
 340 345 350
 Phe Thr Glu Glu Asp Leu Ser Glu Ile Asp Phe Thr Val Gln Gly Lys
 355 360 365
 Thr Gly Gly Cys Gly Ser Cys Ala Leu Gly Asp Ala Phe Arg Cys Asp
 370 375 380
 Gly Cys Pro Tyr Leu Gly Leu Pro Pro Phe Lys Pro Gly Glu Val Val
 385 390 395 400
 Lys Leu Asp Gly Phe Gly Glu Asp Ile
 405

<210> 93

<211> 327

<212> PRT

<213> Candida albicans

<400> 93

Met Ile Arg Thr Ile Lys Pro Lys Asn Ala Arg Ser Lys Arg Ala Leu
 1 5 10 15
 Ala Lys Lys Glu Ala Lys Leu Val Glu Asn Thr Lys Ser Ala Leu Phe
 20 25 30
 Val Pro Gly Ser Thr Gly Asn Lys Phe Leu His Asp Ala Met Cys Asp
 35 40 45
 Leu Met Ala Phe Lys Lys Pro Phe Ala Lys Lys Phe Ser Lys Lys Asn
 50 55 60
 Glu Ile Arg Pro Phe Glu Asp Ser Ser Gln Leu Glu Phe Phe Ala Glu
 65 70 75 80
 Lys Asn Asp Ser Ser Leu Met Val Phe Ser Ser Asn Asn Lys Lys Arg
 85 90 95
 Pro Lys Thr Leu Thr Phe Val Arg Phe Phe Asn Phe Lys Val Tyr Asp
 100 105 110
 Met Ile Gly Leu Ser Ile Gln Glu Asn His Lys Leu Leu Gln Asp Phe
 115 120 125
 Lys Lys Leu Thr Phe Thr Ile Gly Leu Lys Pro Met Phe Val Phe Asn
 130 135 140
 Gly Pro Ile Phe Asp Ser His Pro Val Tyr Gln His Ile Lys Ser Leu
 145 150 155 160
 Phe Leu Asp Phe Phe Arg Gly Glu Glu Thr Asp Leu Gln Asp Val Ala
 165 170 175
 Gly Leu Gln Tyr Val Ile Ala Leu Ser Ala Gly Glu Val Glu Asp Leu
 180 185 190
 Asn Asn Asp Lys Val Leu Pro Leu Val His Phe Arg Val Tyr Lys Leu
 195 200 205
 Lys Ser Tyr Lys Ser Gly Gln Lys Leu Pro Arg Ile Glu Leu Asp Glu
 210 215 220
 Ile Gly Pro Arg Phe Asp Phe Lys Ile Gly Arg Arg Ile Thr Pro Thr
 225 230 235 240

Pro Asp Val Glu Lys Glu Ala Thr Lys Lys Pro Lys Gln Leu Glu Ala
 245 250 255
 Lys Val Lys Lys Asn Val Thr Thr Asp Phe Met Gly Asp Lys Val Ala
 260 265 270
 Gln Ile His Val Gly Lys Gln Asp Leu Ser Lys Leu Gln Thr Arg Lys
 275 280 285
 Met Lys Gly Leu Lys Glu Lys Tyr Asp Gln Glu Ser Glu Glu Glu Asp
 290 295 300
 Val Tyr Val Ser Asp Glu Glu Tyr Phe Gly Glu Asp Ile Glu Glu Pro
 305 310 315 320
 Glu Thr Lys Arg Gln Lys Val
 325

<210> 94

<211> 125

<212> PRT

<213> Candida albicans

<400> 94

Met Ser Lys Thr Asn Thr Ala Ile Tyr Gln Lys Ile Ala Glu Lys Arg
 1 5 10 15
 Ala Asn Leu Glu Arg Phe Arg Glu Phe Lys Glu Leu Thr Asp Asp Leu
 20 25 30
 Val Leu Gln Leu Glu Ser Ile Gly Asp Lys Leu Glu Thr Met Asn Gly
 35 40 45
 Gly Thr Ala Ser Val Ala Leu Ile Leu Ala Asn Trp Lys Ser Val Val
 50 55 60
 Gln Ser Ile Ser Leu Ala Ser Leu Ala Leu Met Lys Glu Ser Asn Asp
 65 70 75 80
 Asn Asn Lys Glu Ala Phe Pro Glu Pro Leu Val Arg Val Arg Val Gly
 85 90 95
 Gln Ser Asn Glu Glu Asn Gln Asp Asp Glu Glu Ala Asp Glu Glu Glu
 100 105 110
 Gly Val Arg Asp Ser Glu Glu Val Glu Glu Ser Thr Glu
 115 120 125

<210> 95

<211> 1120

<212> PRT

<213> Candida albicans

<400> 95

Met Asp Tyr Gln Asp Leu Leu His Lys Ile Ile Lys Glu Phe His Ser
 1 5 10 15
 Leu Lys Glu Phe Lys Pro Trp Asp Ser Ser Val Leu Tyr Glu Thr Leu
 20 25 30
 Leu Arg Ser Val Leu Thr Thr Leu Ile Glu Leu Leu Gly Ile Asp Asn
 35 40 45
 Pro Pro Ser Tyr Leu His Leu Thr Thr Asn Asn Asp Ser Ile Gly Asp
 50 55 60
 Leu Lys Ile Lys Tyr Tyr Gly Asn Ala Leu Ser Lys Ser Ile Asn Gly
 65 70 75 80
 His Ser Met Leu Gln Tyr Leu Glu Ser Lys His Val Ser Ile Leu Gln
 85 90 95
 Ala Val Val Glu Ile Ile Asn Thr Arg Ser Tyr Arg Ile Lys Glu Ser
 100 105 110
 Tyr Ser Ala Val Phe Lys Asp Val Ser His Leu Phe Glu Lys Leu Leu
 115 120 125

Lys Glu Arg Tyr Glu Ala Glu Ser Asn Leu Glu Asp Tyr Ile Leu Gln
 130 135 140
 Cys Leu Met Tyr Glu Thr Gln Phe Tyr Gln Gly Ile Val Asp Asn Val
 145 150 155 160
 Leu Thr Ala Asp Asp Thr Glu Lys Leu Ala Ser Phe Leu Gly Thr Arg
 165 170 175
 Leu Ser Glu Glu Asp Ser Met Phe Ser Tyr Arg Asp Ile Asp Tyr Pro
 180 185 190
 Leu Glu Leu Asn Ile Asn Asn Glu Ser Leu Glu Lys Ile Tyr Lys Ile
 195 200 205
 Phe Leu Gly Val Ile Gly Thr Lys Arg Phe Asp Ile Lys Glu Val Ala
 210 215 220
 Ser Ala Val Val Gly Val Tyr Lys Arg His Gln Arg Ile Asp His Phe
 225 230 235 240
 Glu Lys Leu Asp Ser Asp Glu Ile Leu Gly Lys Phe Phe Arg Asn Ile
 245 250 255
 Leu Pro Gln Ser Phe Gln Ser Val Thr Asn Lys Val Phe Arg Glu Phe
 260 265 270
 His Lys Glu Val Asp Asp Pro Pro Ser Asp Val Leu Asp Gln Leu Asp
 275 280 285
 Asn Ile Val Asp Asp Phe Ile Ala Val Gly Ile Glu Gly Val Asp Leu
 290 295 300
 Gly Phe Pro Ala Leu Phe Arg His Tyr Ile Lys Phe Met Asn Glu Ile
 305 310 315 320
 Phe Pro Thr Val Val Glu Asp Ala Asp Arg Asp Phe Val Ala Arg Ile
 325 330 335
 Asn Ser Leu Ile Ala Gln Val Leu Glu Phe Lys Asp Asp Glu Lys Ser
 340 345 350
 Cys Asp Ile Asn Gln Val Val Ser Glu Phe Val Ser Leu Gln Ser Leu
 355 360 365
 Leu Leu Lys Asn Asn Tyr Leu Ser Pro Ser Thr Leu Leu Met Arg Ala
 370 375 380
 Ser Thr His Asp Tyr Tyr Lys Asn Leu Gln Ile Val Lys Ile Thr Phe
 385 390 395 400
 Asp Gly Trp Asn Glu Asn Ser Lys Arg Ile Leu Lys Leu Glu Asn Ser
 405 410 415
 Gly Phe Leu Gln Ser Lys Thr Leu Pro Lys Tyr Leu Lys Leu Trp Tyr
 420 425 430
 Ser Lys Ser Met Lys Leu Asn Glu Leu Cys Asn Arg Val Asp Glu Phe
 435 440 445
 Tyr Asn Gly Glu Leu Cys Arg Lys Val Trp His Cys Trp Arg Ser Gln
 450 455 460
 Gln Asn Val Tyr Asn Leu Lys Met Glu Val Ala Asp Lys Arg Leu Leu
 465 470 475 480
 Asn Gln Tyr Tyr Ile Lys Trp Arg Lys Lys Glu Lys Asp Met Lys Ala
 485 490 495
 Asn Leu Thr Ile Ala Val Glu Phe Asp His Phe His Leu Leu Asp Lys
 500 505 510
 Ser Phe Lys Ile Leu Lys Gly Tyr Phe Asn Leu Ala Lys Asn Ser Asp
 515 520 525
 Val Leu Ala Met Ser Leu Phe Gln Ser Phe Glu Glu Asn Arg Asp Ser
 530 535 540
 Arg Ile Lys Leu Lys Tyr Phe Gln Tyr Trp Asn Leu Lys Ile Ser Asp
 545 550 555 560
 Arg Val His Gly Leu Thr Met Lys Leu Glu Lys Phe His Gln Val Lys
 565 570 575
 Asp Lys Phe Val Leu Gly Asn Tyr Phe Glu Thr Trp Tyr Tyr Lys His
 580 585 590

Asn Leu Val Glu Lys Ser Asn Asn Phe Val Ser Ala Lys Asp Leu Gln
 595 600 605
 Leu Leu Ala Lys Thr Phe Thr Asn Thr Trp Leu Lys Lys Phe Leu Leu
 610 615 620
 Tyr Lys Lys Ala Phe Lys Ile Glu Glu Glu Leu Gly Ala Asp Leu Lys
 625 630 635 640
 Arg Lys Thr Phe Asp Arg Trp Lys Glu Ala Val Gln Leu Glu Val Lys
 645 650 655
 Ala Lys Glu Phe His Glu Arg His Leu Leu Glu Thr Ala Phe His Glu
 660 665 670
 Trp Lys Leu Lys Ser Ile Leu Ile Ser Asn Arg Ala Ser Phe Asp His
 675 680 685
 Ile Leu Val Gln Arg Cys Phe Gln Thr Trp Ser Val Glu Ile Lys Leu
 690 695 700
 Arg Glu Leu Gln Gln Lys Gln Asp Thr Arg Leu Val Val Asn Ile Phe
 705 710 715 720
 Gln Lys Trp Arg Thr Arg Gln Leu Glu Leu Ala Lys Leu Asp Glu Lys
 725 730 735
 Ser Gln Ala Phe Tyr Glu Ser Asn Met Lys His Leu Val Val Gln Lys
 740 745 750
 Trp Asn Val Glu Asn Ser Asn Ile Gly Leu Leu Glu Lys Arg Ala Asp
 755 760 765
 Arg Phe Phe Ile Arg Arg Phe Phe Ile Gln Lys Trp Gln Ser Lys Met
 770 775 780
 Thr Lys Tyr Glu Asp Ile Thr Val Tyr His Leu Glu Asp Glu Ile Ala
 785 790 795 800
 Thr Lys Leu Ala Tyr Lys Val Trp Arg Gln Arg Tyr Phe Glu Asn Tyr
 805 810 815
 Glu Glu Lys Leu Asp Asn Leu Leu Glu Thr Met Asp Thr Ser Ala Ala
 820 825 830
 Asp Thr Val Arg Cys Ser Arg Tyr Phe Gly Leu Trp Arg Ala Lys Leu
 835 840 845
 Gln Thr Val Lys Gln Ile Glu Glu Arg Val Ser Thr Ser Val Ala Pro
 850 855 860
 Ser Val Ala Ile His Phe Lys Asn Trp His Val Lys Ser Gln Gln Lys
 865 870 875 880
 Gln Glu Leu Leu Glu Asn Ala Leu Gln Phe Glu Glu Ile Asn Leu Ser
 885 890 895
 Arg Phe Leu Leu Ile Trp Phe Gln Arg Leu Gln Glu Val Ser Gln Leu
 900 905 910
 Glu Asp Gln Ala Glu Asp Leu Leu Ala Gln Thr Asn Phe Asn Leu Leu
 915 920 925
 Arg Asn Ala Val His Lys Trp Ser Met Leu Tyr Asn Lys Asn Ile Lys
 930 935 940
 Arg His Lys Gln Leu Cys Glu Asp Phe Ile Ala Arg Lys Glu Thr Ala
 945 950 955 960
 Lys Val Arg Ser Ile Phe Asp Leu Trp Leu Tyr Lys Ile Lys Glu Ile
 965 970 975
 Glu Ala Asn Thr Thr Ile Ile Ser Asn Pro Ser Pro Leu Ser Lys Arg
 980 985 990
 Phe Gln His Gln Arg Glu Met Gly Leu Thr Pro Gln Lys Lys Asn Ser
 995 1000 1005
 Pro Thr Lys Val Phe Thr Pro Thr Thr Ser Lys Asp Pro Ser Pro Thr
 1010 1015 1020
 Lys Leu Gln Glu Thr Thr Gln Arg Met Arg Asn Gln Asn Ile Ser Ala
 1025 1030 1035 1040
 Leu Arg Glu His Phe Gly Arg Ala Arg Ala Ser Ser Thr Pro Lys Lys
 1045 1050 1055

Leu Ser Pro Val Arg Leu Ser Tyr Thr Asn Ile Pro Ser Asn Leu Arg
 1060 1065 1070
 Pro Gln Ser Pro Pro Lys Phe Asp Asp Ser Asp Ile Ala Thr Ala Lys
 1075 1080 1085
 Ser Leu Gly Arg Ile Arg Pro Met Val Phe Pro Ile Asp Asp Gln Ala
 1090 1095 1100
 Asn Phe Ser Pro Met Asp Arg Thr Lys Leu Gln Ser Arg Asn Ala Met
 1105 1110 1115 1120

<210> 96

<211> 745

<212> PRT

<213> Candida albicans

<400> 96

Met Ala Lys Arg Lys Ser Lys Gln Gln Asp Leu Glu Lys Lys Lys Lys
 1 5 10 15
 Leu Lys Gln Ser Gln Asp Glu Gln Leu Ser Thr Gly Leu Phe Asn Asn
 20 25 30
 Val Gly Gln Gly Gln His Gln Gly Asp Asp Asp Asp Glu Glu Gly Asp
 35 40 45
 Glu Ile Asp Trp Asp Asn Gln Glu Met Asp Tyr Glu Leu Ile Pro Arg
 50 55 60
 Lys Ile Thr Thr Lys Lys Thr Ile Glu Ala Leu Pro Ile Lys Lys Ser
 65 70 75 80
 Asp Gly Thr Ile Glu Arg Val Val Arg Glu Val Glu Glu Glu Glu
 85 90 95
 Glu Glu Glu Glu Glu Glu Pro Glu Glu Pro Glu Leu Glu Asn Asp
 100 105 110
 Val Glu Asn Glu Pro Ser Lys Gln Glu Asn Lys Glu Asn Lys Glu Glu
 115 120 125
 Gly Asp Ile Asp Thr Asp Asp Thr Leu Thr Pro Gln Glu Lys Leu Ile
 130 135 140
 Gln Thr Lys Glu Glu Ile Ala Glu Leu Gly Ser Lys Leu Ile Glu Asp
 145 150 155 160
 Pro Glu Glu Asn Ile Val Cys Leu Thr Arg Leu Arg Lys Met Ser Glu
 165 170 175
 Ser Lys Asn Phe Met Thr Ser Gln Leu Ser Ile Leu Ala Leu Ile Pro
 180 185 190
 Ile Phe Lys Ser Leu Ala Pro Ser Tyr Lys Ile Arg Pro Leu Thr Asp
 195 200 205
 Thr Glu Lys Arg Glu Lys Val Ser Arg Glu Ile Ala Lys Leu Arg Asn
 210 215 220
 Phe Glu Gln Asn Leu Val Ile Asn Tyr Lys Ala Tyr Ile Glu Leu Leu
 225 230 235 240
 Thr Lys Tyr Ser Lys Ile Ser Tyr Ser Asn Ser Met Asn Asn Asn Lys
 245 250 255
 Ile Thr Ser Asp Gln Leu Lys Arg Gly Asn Ile Ala Leu Lys Ala Ala
 260 265 270
 Thr Glu Leu Cys Leu Ser Ser Leu Arg His Phe Asn Phe Arg Glu Glu
 275 280 285
 Leu Phe Thr Ile Ile Ile Lys Arg Leu Asn Lys Lys Pro Gln His Gln
 290 295 300
 Gln Asp Tyr Pro Ile Phe Ile Lys Ser Leu Arg Val Leu Glu Thr Leu
 305 310 315 320
 Leu Lys Asp Asp Ala Glu His Gly Asp Ile Thr Phe Asp Ile Ile Lys
 325 330 335

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Ile Met Thr Lys Ser Ile Lys Asp Lys Lys Phe Arg Val Asp Glu Ser
      340                      345                      350
Val Val Asn Val Phe Leu Ser Ile Ser Leu Leu Glu Asp Tyr Asp Pro
      355                      360                      365
Asn Asn Asn Asn Asn Asn Lys Asp Asp His His Asn Thr Thr Leu Lys
      370                      375                      380
Pro Lys Leu Lys Lys Lys Asp Arg Ile His Leu Ser Lys Lys Glu Arg
      385                      390                      395                      400
Lys Ala Arg Lys Glu Arg Lys Glu Ile Glu Glu Glu Ile Gln Lys Ala
      405                      410                      415
Glu Gln Ala Ile Thr Val Glu Gln Arg Glu Lys Tyr Gln Ala Gln Val
      420                      425                      430
Leu Lys Met Val Leu Thr Leu Tyr Leu Glu Ile Leu Lys Ala Gly Ser
      435                      440                      445
Ser Ser Ser Gln Leu Ile Asp Gly Asp Gly Lys Lys Thr Lys Asn Asp
      450                      455                      460
Ala Ser Leu Leu Met Gly Ala Val Leu Glu Gly Leu Ser Arg Phe Gly
      465                      470                      475                      480
Gln Met Ser Asn Leu Asp Leu Leu Gly Asp Phe Leu Glu Val Leu Arg
      485                      490                      495
Glu Ile Met Thr Asp Ile Ile Glu Glu His Lys Gln Ser Gly Asp Asn
      500                      505                      510
Asp Asn Asp Asn Asp Asn Asp Asp Glu Ser Gly Gly Met Tyr Ser Gly
      515                      520                      525
Asn Glu Leu Arg Thr Ile Leu Leu Cys Ile Ala Thr Ser Phe Ser Leu
      530                      535                      540
Val Leu Asn His Asn Ser Met Gly Lys Leu Pro Met Ala Ile Asp Leu
      545                      550                      555                      560
Ser Lys Phe Val Ser Thr Leu Tyr Ile Ile Leu Thr Asp Leu Ala Leu
      565                      570                      575
Asp Pro Asp Leu Glu Phe Ser His Lys Thr Leu Arg Leu Ala Asp Pro
      580                      585                      590
Leu Ser Ser Ser Ser Leu Ser Asn Glu Leu Glu Asn Asn Lys Pro Ala
      595                      600                      605
Val Asn Val Ser Thr Lys Ala Glu Leu Leu Leu Arg Cys Leu Asp Phe
      610                      615                      620
Ile Phe Phe Arg Ser Lys Asn Gly Thr Ile Pro Arg Ala Thr Ala Phe
      625                      630                      635                      640
Ile Lys Arg Leu Tyr Ile Leu Thr Leu Gln Thr Pro Glu Lys Thr Ser
      645                      650                      655
Leu Ala Asn Leu Lys Phe Ile Gly Lys Leu Met Asn Arg Tyr Gly Glu
      660                      665                      670
Asn Ile Lys Gly Leu Trp Asn Thr Glu Glu Arg Ile Ser Gly Glu Gly
      675                      680                      685
Asn Tyr Ile Leu Gly Ile Glu Arg Gln Asn Lys Asp Lys Asp Val Glu
      690                      695                      700
Leu Glu Arg Ser Asn Ser Gly Ala Ala Thr Leu Trp Glu Asn Val Leu
      705                      710                      715                      720
Leu Asp Lys His Tyr Ser Ile Met Ile Lys Asp Gly Ser Arg Ser Leu
      725                      730                      735
Met Lys Asn Ser Lys Ala Asn Thr Asn
      740                      745

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<210> 97

<211> 579

<212> PRT

<213> Candida albicans

<400> 97

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Met Tyr Ile Thr Pro Asn Gln Tyr Ala Lys Thr Phe Gln Asp Ile Lys
 1           5           10           15
Arg Ser Ser Leu Ser His Ser Thr Cys Lys Leu Val Ile Phe Val Ser
      20           25           30
Cys Leu Asp Val Asp Ala Leu Cys Ala Ala Lys Ile Leu Ser Leu Leu
      35           40           45
Leu Arg Lys Glu Leu Ile Gln Tyr Gln Leu Ile Pro Thr Thr Gly Tyr
      50           55           60
Ser Asp Leu Lys Leu His Tyr Asp Lys Leu Asp Ser Glu Val Thr Asn
65           70           75           80
Ile Ile Leu Ile Gly Cys Gly Ala Met Leu Asp Leu Glu Gly Phe Phe
      85           90           95
Asp Val Asn Pro Glu Glu Phe Leu Gly Asp Asn Ser Thr Thr Asn Gly
      100          105          110
His Thr Ile Asp Asn Asp Thr Glu Leu Glu Leu Asp Ala Val Lys Thr
      115          120          125
Asp Asn Phe Ala Leu Thr Arg Lys Ile Tyr Val Val Asp Gly His Arg
      130          135          140
Pro Trp Asn Leu Asp Asn Leu Phe Gly Ser Ala Met Val Val Cys Leu
      145          150          155          160
Asp Asn Gly Tyr Ile Asp Gly Asn Leu Asn Glu Glu Lys Glu Ala Tyr
      165          170          175
Asn Val Leu Val Glu Met Ser Asp Ser Glu Asp Glu Asp Glu Asp Glu
      180          185          190
Gly His Asn Gln Asn Gly His Thr Asp Asp Asp Gln Glu Gly Asp Lys
      195          200          205
Thr Asp Ala Asp Asp Glu Asn Asp Glu Ser Ser Val Ser Thr Ser Arg
      210          215          220
Lys Gly Val Lys Ser Ile Asn Glu Asp Lys Ile Gln Thr Tyr Tyr Asn
      225          230          235          240
Gln Ser Ser Thr Ile Ala Ser Ser Cys Ser Ile Thr Val Tyr Ala Leu
      245          250          255
Val Ser Ala Ile Gly Glu Thr Asn Val Asp Asn Leu Trp Leu Gly Ile
      260          265          270
Val Gly Ala Ser Gly Phe Asp Cys Ser Ile Phe Val Asp Glu Val Arg
      275          280          285
Arg Phe Ser Thr Asp Ser Gly Ile His Met Glu Arg Gly Thr Tyr Leu
      290          295          300
Pro Leu Leu Arg His Ser Ser Leu Tyr Asp Ala Leu Leu Tyr Asn Trp
      305          310          315          320
Ile Asp Gly Asp Lys Arg Ile His Lys Ile Leu Ala Lys Met Gly Val
      325          330          335
Pro Ile Val Ala Ala Lys Gln Gln Trp Gln Tyr Leu Asp Pro Pro Ile
      340          345          350
Lys Asn Lys Leu Pro Gly Leu Leu Lys Lys Tyr Leu Pro Glu Leu Pro
      355          360          365
Gln Val Glu Ile Phe Tyr Arg Cys Gly Val Thr Ser Met Asp Val Phe
      370          375          380
Val Ser Leu Thr Ala Leu Leu Glu Thr Gly Val Gly Leu Asn Asn Thr
      385          390          395          400
Ser Ala Asn Ser Ile Asp His Gly Asp Leu Glu Asp Glu Asn Glu Leu
      405          410          415
Ile Arg Arg Glu Ile Lys Ser Arg Glu Ser Ser Tyr Ile Arg Asn Phe
      420          425          430
Trp Ser Ala Phe Asp Ser Val Ser Ser Phe Gly Ile Ser Asn Asn Ile
      435          440          445

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Gly Leu Glu Lys Gly Ile Thr Ala Ala Lys Leu Val Gln Lys Glu Leu
 450 455 460
 Phe Gln Thr Ile Lys Tyr Ile Ile Glu Gln Lys Leu Ile Lys Asn Leu
 465 470 475 480
 Lys Val Tyr Arg Leu Cys Ile Leu Lys Asp Glu Ser Ser His Ser Gly
 485 490 495
 Phe Asp Asn Pro Val Leu Leu Ile Lys Leu Ser Asn Arg Ile Met Asp
 500 505 510
 Tyr Leu Lys Gln Gln Thr Ser Lys Pro Leu Val Val Ala Ala Glu Leu
 515 520 525
 Ser Asn Thr Tyr Phe Val Leu Gly Met Gly Ile Asn Asn Ala Phe Ser
 530 535 540
 Lys Ile Ser Gly Ala Gln Met Lys Lys Asp Phe Phe Glu Ala Ser Leu
 545 550 555 560
 Val Glu Ile Lys Lys Glu Asp Leu Ala Pro Phe Leu Glu Gln Leu Thr
 565 570 575
 Phe Asn Leu

<210> 98
 <211> 1897
 <212> PRT
 <213> Candida albicans

<400> 98
 Met Ser Tyr Asn Asp Asn Asn Asn His Tyr Tyr Asp Pro Asn Gln Gln
 1 5 10 15
 Gly Gly Met Pro Pro His Gln Gly Gly Glu Gly Tyr Tyr Gln Gln Gln
 20 25 30
 Tyr Asp Asp Met Gly Gln Gln Pro His Gln Gln Asp Tyr Tyr Asp Pro
 35 40 45
 Asn Ala Gln Tyr Gln Gln Gln Pro Tyr Asp Met Asp Gly Tyr Gln Asp
 50 55 60
 Gln Ala Asn Tyr Gly Gly Gln Pro Met Asn Ala Gln Gly Tyr Asn Ala
 65 70 75 80
 Asp Pro Glu Ala Phe Ser Asp Phe Ser Tyr Gly Gly Gln Thr Pro Gly
 85 90 95
 Thr Pro Gly Tyr Asp Gln Tyr Gly Thr Gln Tyr Thr Pro Ser Gln Met
 100 105 110
 Ser Tyr Gly Gly Asp Pro Arg Ser Ser Gly Ala Ser Thr Pro Ile Tyr
 115 120 125
 Gly Gly Gln Gly Gln Gly Tyr Asp Pro Thr Gln Phe Asn Met Ser Ser
 130 135 140
 Asn Leu Pro Tyr Pro Ala Trp Ser Ala Asp Pro Gln Ala Pro Ile Lys
 145 150 155 160
 Ile Glu His Ile Glu Asp Ile Phe Ile Asp Leu Thr Asn Lys Phe Gly
 165 170 175
 Phe Gln Arg Asp Ser Met Arg Asn Met Phe Asp Tyr Phe Met Thr Leu
 180 185 190
 Leu Asp Ser Arg Ser Ser Arg Met Ser Pro Ala Gln Ala Leu Leu Ser
 195 200 205
 Leu His Ala Asp Tyr Ile Gly Gly Asp Asn Ala Asn Tyr Arg Lys Trp
 210 215 220
 Tyr Phe Ser Ser Gln Gln Asp Leu Asp Asp Ser Leu Gly Phe Ala Asn
 225 230 235 240
 Met Thr Leu Gly Lys Ile Gly Arg Lys Ala Arg Lys Ala Ser Lys Lys
 245 250 255

Ser Lys Lys Ala Arg Lys Ala Ala Glu Glu His Gly Gln Asp Val Asp
 260 265 270
 Ala Leu Ala Asn Glu Leu Glu Gly Asp Tyr Ser Leu Glu Ala Ala Glu
 275 280 285
 Ile Arg Trp Lys Ala Lys Met Asn Ser Leu Thr Pro Glu Glu Arg Val
 290 295 300
 Arg Asp Leu Ala Leu Tyr Leu Leu Ile Trp Gly Glu Ala Asn Gln Val
 305 310 315 320
 Arg Phe Thr Pro Glu Cys Leu Cys Tyr Ile Tyr Lys Ser Ala Thr Asp
 325 330 335
 Tyr Leu Asn Ser Pro Leu Cys Gln Gln Arg Gln Glu Pro Val Pro Glu
 340 345 350
 Gly Asp Tyr Leu Asn Arg Val Ile Thr Pro Leu Tyr Arg Phe Ile Arg
 355 360 365
 Ser Gln Val Tyr Glu Ile Tyr Asp Gly Arg Phe Val Lys Arg Glu Lys
 370 375 380
 Asp His Asn Lys Val Ile Gly Tyr Asp Asp Val Asn Gln Leu Phe Trp
 385 390 395 400
 Tyr Pro Glu Gly Ile Ser Arg Ile Ile Phe Glu Asp Gly Thr Arg Leu
 405 410 415
 Val Asp Ile Pro Gln Glu Glu Arg Phe Leu Lys Leu Gly Glu Val Glu
 420 425 430
 Trp Lys Asn Val Phe Phe Lys Thr Tyr Lys Glu Ile Arg Thr Trp Leu
 435 440 445
 His Phe Val Thr Asn Phe Asn Arg Ile Trp Ile Ile His Gly Thr Ile
 450 455 460
 Tyr Trp Met Tyr Thr Ala Tyr Asn Ser Pro Thr Leu Tyr Thr Lys His
 465 470 475 480
 Tyr Val Gln Thr Ile Asn Gln Gln Pro Leu Ala Ser Ser Arg Trp Ala
 485 490 495
 Ala Cys Ala Ile Gly Gly Val Leu Ala Ser Phe Ile Gln Ile Leu Ala
 500 505 510
 Thr Leu Phe Glu Trp Ile Phe Val Pro Arg Glu Trp Ala Gly Ala Gln
 515 520 525
 His Leu Ser Arg Arg Met Leu Phe Leu Val Leu Ile Phe Leu Leu Asn
 530 535 540
 Leu Val Pro Pro Val Tyr Thr Phe Gln Ile Thr Lys Leu Val Ile Tyr
 545 550 555 560
 Ser Lys Ser Ala Tyr Ala Val Ser Ile Val Gly Phe Phe Ile Ala Val
 565 570 575
 Ala Thr Leu Val Phe Phe Ala Val Met Pro Leu Gly Gly Leu Phe Thr
 580 585 590
 Ser Tyr Met Asn Lys Arg Ser Arg Arg Tyr Ile Ala Ser Gln Thr Phe
 595 600 605
 Thr Ala Asn Tyr Ile Lys Leu Lys Gly Leu Asp Met Trp Met Ser Tyr
 610 615 620
 Leu Leu Trp Phe Leu Val Phe Leu Ala Lys Leu Val Glu Ser Tyr Phe
 625 630 635 640
 Phe Ser Thr Leu Ser Leu Arg Asp Pro Ile Arg Asn Leu Ser Thr Met
 645 650 655
 Thr Met Arg Cys Val Gly Glu Val Trp Tyr Lys Asp Ile Val Cys Arg
 660 665 670
 Asn Gln Ala Lys Ile Val Leu Gly Leu Met Tyr Leu Val Asp Leu Leu
 675 680 685
 Leu Phe Phe Leu Asp Thr Tyr Met Trp Tyr Ile Ile Cys Asn Cys Ile
 690 695 700
 Phe Ser Ile Gly Arg Ser Phe Tyr Leu Gly Ile Ser Ile Leu Thr Pro
 705 710 715 720

Trp Arg Asn Ile Phe Thr Arg Leu Pro Lys Arg Ile Tyr Ser Lys Ile
 725 730 735
 Leu Ala Thr Thr Glu Met Glu Ile Lys Tyr Lys Pro Lys Val Leu Ile
 740 745 750
 Ser Gln Ile Trp Asn Ala Ile Val Ile Ser Met Tyr Arg Glu His Leu
 755 760 765
 Leu Ala Ile Asp His Val Gln Lys Leu Leu Tyr His Gln Val Pro Ser
 770 775 780
 Glu Ile Glu Gly Lys Arg Thr Leu Arg Ala Pro Thr Phe Phe Val Ser
 785 790 795 800
 Gln Asp Asp Asn Asn Phe Glu Thr Glu Phe Phe Pro Arg Asn Ser Glu
 805 810 815
 Ala Glu Arg Arg Ile Ser Phe Phe Ala Gln Ser Leu Ala Thr Pro Met
 820 825 830
 Pro Glu Pro Leu Pro Val Asp Asn Met Pro Thr Phe Thr Val Phe Thr
 835 840 845
 Pro His Tyr Ser Glu Lys Ile Leu Leu Ser Leu Arg Glu Ile Ile Arg
 850 855 860
 Glu Asp Asp Gln Phe Ser Arg Val Thr Leu Leu Glu Tyr Leu Lys Gln
 865 870 875 880
 Leu His Pro Val Glu Trp Asp Cys Phe Val Lys Asp Thr Lys Ile Leu
 885 890 895
 Ala Glu Glu Thr Ala Ala Tyr Glu Asn Gly Asp Asp Ser Glu Lys Leu
 900 905 910
 Ser Glu Asp Gly Leu Lys Ser Lys Ile Asp Asp Leu Pro Phe Tyr Cys
 915 920 925
 Ile Gly Phe Lys Ser Ala Ala Pro Glu Tyr Thr Leu Arg Thr Arg Ile
 930 935 940
 Trp Ala Ser Leu Arg Ser Gln Thr Leu Tyr Arg Thr Val Ser Gly Phe
 945 950 955 960
 Met Asn Tyr Ala Arg Ala Ile Lys Leu Leu Tyr Arg Val Glu Asn Pro
 965 970 975
 Glu Leu Val Gln Tyr Phe Gly Gly Asp Pro Glu Gly Leu Glu Leu Ala
 980 985 990
 Leu Glu Arg Met Ala Arg Arg Lys Phe Arg Phe Leu Val Ser Met Gln
 995 1000 1005
 Arg Leu Ser Lys Phe Lys Asp Asp Glu Met Glu Asn Ala Glu Phe Leu
 1010 1015 1020
 Leu Arg Ala Tyr Pro Asp Leu Gln Ile Ala Tyr Leu Asp Glu Glu Pro
 1025 1030 1035 1040
 Ala Leu Asn Glu Asp Glu Glu Pro Arg Val Tyr Ser Ala Leu Ile Asp
 1045 1050 1055
 Gly His Cys Glu Met Leu Glu Asn Gly Arg Arg Arg Pro Lys Phe Arg
 1060 1065 1070
 Val Gln Leu Ser Gly Asn Pro Ile Leu Gly Asp Gly Lys Ser Asp Asn
 1075 1080 1085
 Gln Asn His Ala Val Ile Phe His Arg Gly Glu Tyr Ile Gln Leu Ile
 1090 1095 1100
 Asp Ala Asn Gln Asp Asn Tyr Leu Glu Glu Cys Leu Lys Ile Arg Ser
 1105 1110 1115 1120
 Val Leu Ala Glu Phe Glu Glu Met Asn Val Glu His Val Asn Pro Tyr
 1125 1130 1135
 Ala Pro Asn Leu Lys Ser Glu Asp Asn Asn Thr Lys Lys Asp Pro Val
 1140 1145 1150
 Ala Phe Leu Gly Ala Arg Glu Tyr Ile Phe Ser Glu Asn Ser Gly Val
 1155 1160 1165
 Leu Gly Asp Val Ala Ala Gly Lys Glu Gln Thr Phe Gly Thr Leu Phe
 1170 1175 1180

Ala Arg Thr Leu Ala Gln Ile Gly Gly Lys Leu His Tyr Gly His Pro
 1185 1190 1195 1200
 Asp Phe Leu Asn Ala Thr Phe Met Leu Thr Arg Gly Gly Val Ser Lys
 1205 1210 1215
 Ala Gln Lys Gly Leu His Leu Asn Glu Asp Ile Tyr Ala Gly Met Asn
 1220 1225 1230
 Ala Met Met Arg Gly Gly Lys Ile Lys His Cys Glu Tyr Tyr Gln Cys
 1235 1240 1245
 Gly Lys Gly Arg Asp Leu Gly Phe Gly Ser Ile Leu Asn Phe Thr Thr
 1250 1255 1260
 Lys Ile Gly Ala Gly Met Gly Glu Gln Met Leu Ser Arg Glu Tyr Phe
 1265 1270 1275 1280
 Tyr Leu Gly Thr Gln Leu Pro Leu Asp Arg Phe Leu Ser Phe Tyr Tyr
 1285 1290 1295
 Gly His Pro Gly Phe His Ile Asn Asn Leu Phe Ile Gln Leu Ser Leu
 1300 1305 1310
 Gln Val Phe Ile Leu Val Leu Gly Asn Leu Asn Ser Leu Ala His Glu
 1315 1320 1325
 Ala Ile Met Cys Ser Tyr Asn Lys Asp Val Pro Val Thr Asp Val Leu
 1330 1335 1340
 Tyr Pro Phe Gly Cys Tyr Asn Ile Ala Pro Ala Val Asp Trp Ile Arg
 1345 1350 1355 1360
 Arg Tyr Thr Leu Ser Ile Phe Ile Val Phe Phe Ile Ser Phe Ile Pro
 1365 1370 1375
 Leu Val Val Gln Glu Leu Ile Glu Arg Gly Val Trp Lys Ala Phe Gln
 1380 1385 1390
 Arg Phe Val Arg His Phe Ile Ser Met Ser Pro Phe Phe Glu Val Phe
 1395 1400 1405
 Val Ala Gln Ile Tyr Ser Ser Ser Val Phe Thr Asp Leu Thr Val Gly
 1410 1415 1420
 Gly Ala Arg Tyr Ile Ser Thr Gly Arg Gly Phe Ala Thr Ser Arg Ile
 1425 1430 1435 1440
 Pro Phe Ser Ile Leu Tyr Ser Arg Phe Ala Asp Ser Ser Ile Tyr Met
 1445 1450 1455
 Gly Ala Arg Leu Met Leu Ile Leu Leu Phe Gly Thr Val Ser His Trp
 1460 1465 1470
 Gln Ala Pro Leu Leu Trp Phe Trp Ala Ser Leu Ser Ala Leu Met Phe
 1475 1480 1485
 Ser Pro Phe Ile Phe Asn Pro His Gln Phe Ala Trp Glu Asp Phe Phe
 1490 1495 1500
 Leu Asp Tyr Arg Asp Phe Ile Arg Trp Leu Ser Arg Gly Asn Thr Lys
 1505 1510 1515 1520
 Trp His Arg Asn Ser Trp Ile Gly Tyr Val Arg Leu Ser Arg Ser Arg
 1525 1530 1535
 Ile Thr Gly Phe Lys Arg Lys Leu Thr Gly Asp Val Ser Glu Lys Ala
 1540 1545 1550
 Ala Gly Asp Ala Ser Arg Ala His Arg Ser Asn Val Leu Phe Ala Asp
 1555 1560 1565
 Phe Leu Pro Thr Leu Ile Tyr Thr Ala Gly Leu Tyr Val Ala Tyr Thr
 1570 1575 1580
 Phe Ile Asn Ala Gln Thr Gly Val Thr Ser Tyr Pro Tyr Glu Ile Asn
 1585 1590 1595 1600
 Gly Ser Thr Asp Pro Gln Pro Val Asn Ser Thr Leu Arg Leu Ile Ile
 1605 1610 1615
 Cys Ala Leu Ala Pro Val Val Ile Asp Met Gly Cys Leu Gly Val Cys
 1620 1625 1630
 Leu Ala Met Ala Cys Cys Ala Gly Pro Met Leu Gly Leu Cys Cys Lys
 1635 1640 1645

Lys Thr Gly Ala Val Ile Ala Gly Val Ala His Gly Val Ala Val Ile
 1650 1655 1660
 Val His Ile Ile Phe Phe Ile Val Met Trp Val Thr Glu Gly Phe Asn
 1665 1670 1675 1680
 Phe Ala Arg Leu Met Leu Gly Ile Ala Thr Met Ile Tyr Val Gln Arg
 1685 1690 1695
 Leu Leu Phe Lys Phe Leu Thr Leu Cys Phe Leu Thr Arg Glu Phe Lys
 1700 1705 1710
 Asn Asp Lys Ala Asn Thr Ala Phe Thr Trp Thr Gly Lys Trp Tyr Asn Thr
 1715 1720 1725
 Gly Met Gly Trp Met Ala Phe Thr Gln Pro Ser Arg Glu Phe Val Ala
 1730 1735 1740
 Lys Ile Ile Glu Met Ser Glu Phe Ala Gly Asp Phe Val Leu Ala His
 1745 1750 1755 1760
 Ile Ile Leu Phe Cys Gln Leu Pro Leu Leu Phe Ile Pro Leu Val Asp
 1765 1770 1775
 Arg Trp His Ser Met Met Leu Phe Trp Leu Lys Pro Ser Arg Leu Ile
 1780 1785 1790
 Arg Pro Pro Ile Tyr Ser Leu Lys Gln Ala Arg Leu Arg Lys Arg Met
 1795 1800 1805
 Val Arg Lys Tyr Cys Val Leu Tyr Phe Ala Val Leu Ile Leu Phe Ile
 1810 1815 1820
 Val Ile Ile Val Ala Pro Ala Val Ala Ser Gly Gln Ile Ala Val Asp
 1825 1830 1835 1840
 Gln Phe Ala Asn Ile Gly Gly Ser Gly Ser Ile Ala Asp Gly Leu Phe
 1845 1850 1855
 Gln Pro Arg Asn Val Ser Asn Asn Asp Thr Gly Asn His Arg Pro Lys
 1860 1865 1870
 Thr Tyr Thr Trp Ser Tyr Leu Ser Thr Arg Phe Thr Gly Ser Thr Thr
 1875 1880 1885
 Pro Tyr Ser Thr Asn Pro Phe Arg Val
 1890 1895

<210> 99

<211> 400

<212> PRT

<213> Candida albicans

<400> 99

Met Ser Phe Arg Thr Thr Ser Met Arg Met Ala Arg Leu Ala Thr Ala
 1 5 10 15
 Lys Ala Thr Leu Ser Lys Arg Thr Phe Ser Leu Leu Ala Asn Ala Thr
 20 25 30
 Thr Arg Tyr Thr Ala Ala Ser Ser Ala Ala Lys Ala Met Thr Pro Ile
 35 40 45
 Thr Ser Ile Arg Gly Val Lys Thr Ile Asn Phe Gly Gly Thr Glu Glu
 50 55 60
 Val Val His Glu Arg Ala Asp Trp Pro Lys Glu Arg Leu Leu Asp Tyr
 65 70 75 80
 Phe Lys Asn Asp Thr Phe Ala Leu Ile Gly Tyr Gly Ser Gln Gly Tyr
 85 90 95
 Gly Gln Gly Leu Asn Leu Arg Asp Asn Gly Leu Asn Val Ile Ile Gly
 100 105 110
 Val Arg Lys Gly Ser Ser Trp Glu Ala Ala Val Glu Asp Gly Trp Val
 115 120 125
 Pro Gly Glu Asn Leu Phe Glu Val Asp Glu Ala Ile Ser Arg Gly Thr
 130 135 140

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Ile Ile Met Asp Leu Leu Ser Asp Ala Ala Gln Ser Glu Thr Trp Phe
145          150          155          160
His Ile Lys Pro Gln Leu Thr Glu Gly Lys Thr Leu Tyr Phe Ser His
          165          170          175
Gly Phe Ser Pro Val Phe Lys Asp Leu Thr His Val Glu Pro Pro Ser
          180          185          190
Asn Ile Asp Val Ile Leu Ala Ala Pro Lys Gly Ser Gly Arg Thr Val
          195          200          205
Arg Ser Leu Phe Lys Glu Gly Arg Gly Ile Asn Ser Ser Tyr Ala Val
          210          215          220
Trp Asn Asp Val Thr Gly Lys Ala Glu Glu Lys Ala Ile Ala Met Ala
225          230          235          240
Ile Ala Ile Gly Ser Gly Tyr Val Tyr Lys Thr Thr Phe Glu Arg Glu
          245          250          255
Val Asn Ser Asp Leu Tyr Gly Glu Arg Gly Cys Leu Met Gly Gly Ile
          260          265          270
His Gly Met Phe Leu Ala Gln Tyr Glu Val Leu Arg Glu Asn Gly His
          275          280          285
Thr Pro Ser Glu Ala Phe Asn Glu Thr Val Glu Glu Ala Thr Gln Ser
          290          295          300
Leu Tyr Pro Leu Ile Gly Lys Tyr Gly Met Asp Tyr Met Tyr Asp Ala
305          310          315          320
Cys Ser Thr Thr Ala Arg Arg Gly Ala Leu Asp Trp Tyr Pro Arg Phe
          325          330          335
Lys Asp Ala Leu Lys Pro Val Phe Glu Glu Leu Tyr Glu Ser Val Lys
          340          345          350
Asn Gly Ser Glu Thr Lys Arg Ser Leu Glu Phe Asn Ser Arg Ser Asp
          355          360          365
Tyr Lys Glu Arg Leu Glu Glu Glu Leu Gln Thr Ile Arg Asn Met Glu
          370          375          380
Ile Trp Arg Val Gly Lys Glu Val Arg Lys Leu Arg Pro Glu Asn Gln
385          390          395          400

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<210> 100

<211> 278

<212> PRT

<213> Candida albicans

<400> 100

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Met Phe Lys Gln Ser Ile Arg Ser Leu Ala Thr Lys Ser Pro Ile Ser
1          5          10          15
Ser Ala Ala Ala Thr Thr Thr Thr Ala Ser Thr Thr Ser Thr Thr Thr
          20          25          30
Thr Ala Ser Leu Asn Phe Ala Lys Pro Pro Ser Tyr Thr Leu Ala Gln
          35          40          45
Leu Arg Glu Phe Pro Ser Leu Glu Pro Lys Thr Phe Ile Pro Leu Pro
          50          55          60
Thr Thr Phe Phe Asn Thr Glu Lys Pro Ile Arg Arg Asp Ile Leu Trp
65          70          75          80
Ser Cys Val Thr Tyr Glu Ala Asp Lys Ala Arg Val Gly Ser Asn Tyr
          85          90          95
Ala Ile Leu Lys Ser Asp Ser Pro Tyr Ser Asn Arg Lys Leu Arg Pro
          100          105          110
Gln Lys Gly Ser Gly Arg Ala Arg Leu Gly Asp Ala Asn Ser Pro His
          115          120          125
Met Asp Asn Glu Ile Lys Ala His Ala Ile Lys Gly Pro His Asp Trp
130          135          140

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Ser Thr Asp Leu Pro Ser Lys Ile Tyr Ser Arg Gly Ile Gln Asn Ala
 145 150 155 160
 Phe Thr Met His Tyr Lys Gln Gly Asn Leu Asn Val Val Glu Asn Glu
 165 170 175
 Leu Asp Phe Gln Tyr Gly Tyr Asp Ile Ile Thr Gln Ser Phe Val Ser
 180 185 190
 Val His Asn Leu Asn Lys Leu Asn Leu Leu Phe Ile Thr Asn Glu Pro
 195 200 205
 Arg Asp Asn Leu Met Glu Ser Ile Lys Lys Phe Tyr Ile Asn Glu Lys
 210 215 220
 Glu Phe Asn Ser Leu Asn Lys Lys Glu Lys Pro Lys Tyr Leu Gln Lys
 225 230 235 240
 Leu Lys Gly Lys Val Leu Thr Lys Glu Asp Val Glu Val Arg Asp Ile
 245 250 255
 Leu Arg Ala His Arg Val Phe Ile Glu Ser Ser Ala Leu Gln Trp Phe
 260 265 270
 Ile Thr Lys His Thr Val
 275

<210> 101

<211> 448

<212> PRT

<213> Candida albicans

<400> 101

Met Arg Glu Val Ile Ser Ile Asn Val Gly Gln Ala Gly Cys Gln Ile
 1 5 10 15
 Gly Asn Ala Cys Trp Glu Leu Tyr Ser Gln Glu His Gly Ile Arg Pro
 20 25 30
 Asp Gly Tyr Leu Gln Glu Gly Leu Asp Arg Pro Lys Gly Gly Glu Glu
 35 40 45
 Gly Phe Ser Thr Phe Phe Ser Glu Thr Gly Ser Gly Lys Tyr Val Pro
 50 55 60
 Arg Ala Leu Tyr Val Asp Leu Glu Pro Asn Val Ile Asp Glu Val Arg
 65 70 75 80
 Thr Gly Val Tyr Lys Asp Leu Phe His Pro Glu Gln Leu Ile Ala Gly
 85 90 95
 Lys Glu Asp Ala Ala Asn Asn Tyr Ala Arg Gly His Tyr Thr Val Gly
 100 105 110
 Arg Glu Ile Leu Asp Asp Ile Leu Asp Arg Val Arg Arg Met Ser Asp
 115 120 125
 Gln Cys Asp Gly Leu Gln Gly Phe Leu Phe Thr His Ser Leu Gly Gly
 130 135 140
 Gly Thr Gly Ser Gly Leu Gly Ser Leu Leu Leu Glu Gln Leu Ser Leu
 145 150 155 160
 Asp Tyr Gly Lys Lys Ser Lys Leu Glu Phe Ala Val Tyr Pro Ala Pro
 165 170 175
 Gln Val Ser Thr Ser Val Val Glu Pro Tyr Asn Thr Val Leu Thr Thr
 180 185 190
 His Thr Thr Leu Glu His Ala Asp Cys Thr Phe Met Val Asp Asn Glu
 195 200 205
 Ala Ile Tyr Asp Met Cys Arg Arg Asn Leu Asp Ile Ala Arg Pro Asn
 210 215 220
 Phe Ser Ser Leu Asn Asn Leu Ile Ala Gln Val Val Ser Ser Val Thr
 225 230 235 240
 Ala Ser Leu Arg Phe Asp Gly Ser Leu Asn Val Asp Leu Asn Glu Phe
 245 250 255

Gln Thr Asn Leu Val Pro Tyr Pro Arg Ile His Phe Pro Leu Val Ser
 260 265 270
 Tyr Ala Pro Val Phe Ser Lys Ser Arg Ala Thr His Glu Ala Asn Ser
 275 280 285
 Val Ser Glu Ile Thr Gln Ser Cys Phe Glu Pro Gly Asn Gln Met Val
 290 295 300
 Lys Cys Asp Pro Arg Thr Gly Lys Tyr Met Ala Thr Cys Leu Leu Tyr
 305 310 315 320
 Arg Gly Asp Val Val Thr Arg Asp Val Gln Asn Ala Val Ala Gln Val
 325 330 335
 Lys Ser Lys Lys Thr Val Gln Leu Val Asp Trp Cys Pro Thr Gly Phe
 340 345 350
 Lys Ile Gly Ile Cys Tyr Gln Pro Pro Thr Ala Ile Lys Gly Ser Glu
 355 360 365
 Leu Ala Ser Ala Ser Arg Ala Val Cys Met Leu Ser Asn Thr Thr Ala
 370 375 380
 Ile Ala Glu Ala Trp Arg Arg Ile Asp Arg Lys Phe Asp Leu Met Tyr
 385 390 395 400
 Ser Lys Arg Ala Phe Val His Trp Tyr Val Gly Glu Gly Met Glu Glu
 405 410 415
 Gly Glu Phe Thr Glu Ala Arg Glu Asp Leu Ala Ala Leu Glu Arg Asp
 420 425 430
 Tyr Ile Glu Val Gly Thr Asp Ser Phe Pro Glu Glu Glu Glu Glu Tyr
 435 440 445

<210> 102

<211> 275

<212> PRT

<213> Candida albicans

<400> 102

Met Lys Thr Ser Val Phe Ile Ala Ile Phe Asn Leu Leu Val Cys Ala
 1 5 10 15
 Leu Ala Tyr Thr Asp Leu Thr Gly Ser Ile Lys Ile Asn Asp Lys Lys
 20 25 30
 Ile Thr Leu Gly Glu Phe Asn Thr Gln Glu Val Lys Gln Leu Thr Ile
 35 40 45
 Asn Ser Pro Lys Asp Ile Ile Glu Ile Asp Leu Lys Ser Lys Asp Ile
 50 55 60
 Lys Gly Lys Pro Glu Gln Ile Met Val Ser Leu Ala Asp Val Lys Asn
 65 70 75 80
 Pro Ala Ile Ser Thr His Tyr Val Pro Val Val Lys Glu Ser Lys Ile
 85 90 95
 Lys Leu Asn Ile Lys Ala Leu Ser Ile Pro Glu Val Leu Lys Thr Lys
 100 105 110
 Asp Lys Leu Val Leu Thr Ile Val Ile Ala Asp Ser Lys Ser Lys Asn
 115 120 125
 Asn Met Ile Arg Arg Leu Val Glu Val Leu Pro Ser Pro Glu Phe Lys
 130 135 140
 Ser Thr Ser Arg Tyr Gln Ala Lys Pro Arg Ile Gly Ile Gln Pro Glu
 145 150 155 160
 Ile His His Ile Phe Arg Glu Asp Glu Arg Thr Val Asn Pro Ile Val
 165 170 175
 Pro Val Val Phe Ile Ile Ala Ala Phe Thr Leu Leu Leu Gly Leu Phe
 180 185 190
 Gly Ser Trp Val Gly Phe Ile Gly Ile Asp Asn Leu Phe Arg Thr Phe
 195 200 205

Lys Thr Ile Ser Lys Val Gln Leu Leu His Asn Val Ser Phe Leu Ile
 210 215 220
 Ser Val Leu Gly Phe Glu Leu Asn Phe Val Lys Tyr Tyr Leu Gly Gln
 225 230 235 240
 Ser Ile Phe Thr Thr Leu Phe Tyr Gly Phe Ile Leu Ser Ile Pro Cys
 245 250 255
 Val Tyr Phe Gly Val Ser Val Leu Arg Ser Leu Ala Lys Asn Arg Ala
 260 265 270
 Leu Gly Lys
 275

<210> 103
 <211> 193
 <212> PRT
 <213> Candida albicans

<400> 103
 Met Leu Met Tyr Thr Ile Leu Ile Pro Ser Leu Leu Tyr Ile Ala Leu
 1 5 10 15
 Thr Ile Ala Ser Ser Glu Leu Leu Asn Ser Ile Gln Gly Thr Trp Gln
 20 25 30
 Ser Gln Ser Glu Arg Val Ile Thr Gly Pro Thr Phe Phe Asp Pro Gln
 35 40 45
 Lys Glu Leu Leu Glu Glu Pro Lys Leu Pro Gly Ile Ser Tyr Ser Phe
 50 55 60
 Lys Asn Gly Tyr Trp Glu Ser Ala Gln Tyr Ile Val Met Gly Asn Asn
 65 70 75 80
 Arg Asn His Gln Cys Pro Gln Ala Met Leu Ile Trp Gln His Gly Lys
 85 90 95
 Tyr Asn Leu Lys Arg Gly Lys Leu Val Leu Ile Pro Asn Arg Asn Asp
 100 105 110
 Gly Arg Gln Leu Ile Ser Asp Pro Cys Leu Asp Asn Gly Lys Ser Glu
 115 120 125
 Tyr Lys Arg Phe His Asn Gly Glu Thr Leu Glu Val Asp Ile Arg Phe
 130 135 140
 Asp Gly Tyr Phe Gly Asn Trp Lys Leu Val Leu Val Asp Tyr Leu Thr
 145 150 155 160
 Gly Lys Lys Lys Gln Pro Met Trp Leu Thr Ser Arg Asn Ala Thr Met
 165 170 175
 Leu Pro Thr Gly Thr Ile Thr Ser Thr Lys Arg Lys Tyr Val Lys Lys
 180 185 190
 Glu

<210> 104
 <211> 432
 <212> PRT
 <213> Candida albicans

<400> 104
 Met Ser Lys Ala Phe Ser Ala Pro Gly Lys Ala Phe Leu Ala Gly Gly
 1 5 10 15
 Tyr Leu Val Leu Glu Pro Ile Tyr Asp Ala Tyr Val Thr Ala Leu Ser
 20 25 30
 Ser Arg Met His Ala Val Ile Thr Pro Lys Gly Thr Ser Leu Lys Glu
 35 40 45
 Ser Arg Ile Lys Ile Ser Ser Pro Gln Phe Ala Asn Gly Glu Trp Glu
 50 55 60

Tyr His Ile Ser Ser Asn Thr Glu Lys Pro Lys Glu Val Gln Ser Arg
 65 70 75 80
 Ile Asn Pro Phe Leu Glu Ala Thr Ile Phe Ile Val Leu Ala Tyr Ile
 85 90 95
 Gln Pro Thr Glu Ala Phe Asp Leu Glu Ile Ile Ile Tyr Ser Asp Pro
 100 105 110
 Gly Tyr His Ser Gln Glu Asp Thr Glu Thr Lys Thr Ser Ser Asn Gly
 115 120 125
 Glu Lys Thr Phe Leu Tyr His Ser Arg Ala Ile Thr Glu Val Glu Lys
 130 135 140
 Thr Gly Leu Gly Ser Ser Ala Gly Leu Val Ser Val Val Ala Thr Ser
 145 150 155 160
 Leu Leu Ser His Phe Ile Pro Asn Val Ile Ser Thr Asn Lys Asp Ile
 165 170 175
 Leu His Asn Val Ala Gln Ile Ala His Cys Tyr Ala Gln Lys Lys Ile
 180 185 190
 Gly Ser Gly Phe Asp Val Ala Thr Ala Ile Tyr Gly Ser Ile Val Tyr
 195 200 205
 Arg Arg Phe Gln Pro Ala Leu Ile Asn Asp Val Phe Gln Val Leu Glu
 210 215 220
 Ser Asp Pro Glu Lys Phe Pro Thr Glu Leu Lys Lys Leu Ile Ala Ser
 225 230 235 240
 Asn Trp Glu Phe Lys His Glu Arg Cys Thr Leu Pro His Gly Ile Lys
 245 250 255
 Leu Leu Met Gly Asp Val Lys Gly Gly Ser Glu Thr Pro Lys Leu Val
 260 265 270
 Ser Arg Val Leu Gln Trp Lys Lys Glu Lys Pro Glu Glu Ser Ser Val
 275 280 285
 Val Tyr Asp Gln Leu Asn Ser Ala Asn Leu Gln Phe Met Lys Glu Leu
 290 295 300
 Arg Glu Met Arg Glu Lys Tyr Asp Ser Asp Pro Glu Thr Tyr Ile Lys
 305 310 315 320
 Glu Leu Asp His Ser Val Glu Pro Leu Thr Val Ala Ile Lys Asn Ile
 325 330 335
 Arg Lys Gly Leu Gln Ala Leu Thr Gln Lys Ser Glu Val Pro Ile Glu
 340 345 350
 Pro Asp Val Gln Thr Gln Leu Leu Asp Arg Cys Gln Glu Ile Pro Gly
 355 360 365
 Cys Val Gly Gly Val Val Pro Gly Ala Gly Gly Tyr Asp Ala Ile Ala
 370 375 380
 Val Leu Val Leu Glu Asn Gln Val Gly Asn Phe Lys Gln Lys Thr Leu
 385 390 395 400
 Glu Asn Pro Asp Tyr Phe His Asn Val Tyr Trp Val Asp Leu Glu Glu
 405 410 415
 Gln Thr Glu Gly Val Leu Glu Glu Lys Pro Glu Asp Tyr Ile Gly Leu
 420 425 430

<210> 105

<211> 768

<212> PRT

<213> Candida albicans

<400> 105

Met Ser Asp Leu Thr Pro Ile Lys Leu Pro Ser Ser Ala Pro Phe Pro
 1 5 10 15
 Val Val Ile Ser Ser Val Leu Cys Lys Pro Gly Asp Thr Ile Ser Lys
 20 25 30

His Lys Thr Ile Phe Lys Tyr Lys Tyr Trp Asp Tyr Gln Asp Asp Pro
 35 40 45
 Thr Ser Lys Glu Asp Pro Pro Lys Lys Ile Arg Val Glu Arg Leu Gly
 50 55 60
 Thr Phe Glu Ser Pro Ile Glu Gly Glu Ile Asp Gln Ile Asn Ile Lys
 65 70 75 80
 Pro Leu Gln Glu Val Met His Ser Asp Val Asp Leu Leu Phe Val Lys
 85 90 95
 Glu Ala Cys Pro His Thr Val Gln Tyr Ser Gly Leu Cys Ala Leu Cys
 100 105 110
 Gly Lys Ser Leu Glu Glu Glu Lys Asp Tyr Ser Gly Tyr Asn Tyr Glu
 115 120 125
 Asp Arg Ala Thr Ile Glu Met Ser His Asp Asn Thr Gly Leu Lys Ile
 130 135 140
 Ser Phe Asp Glu Ala Ala Lys Ile Glu His Asn Thr Thr Asp Arg Leu
 145 150 155 160
 Ile Asp Glu Arg Lys Leu Ile Leu Val Val Asp Leu Asp Gln Thr Val
 165 170 175
 Ile His Ala Thr Val Asp Pro Thr Val Gly Glu Trp Gln Ser Asp Pro
 180 185 190
 Ala Asn Pro Asn Tyr Ala Ala Val Lys Asp Val Lys Thr Phe Cys Leu
 195 200 205
 Glu Glu Glu Ala Ile Val Pro Pro Gly Trp Thr Gly Pro Lys Leu Ala
 210 215 220
 Pro Thr Lys Cys Thr Tyr Tyr Val Lys Leu Arg Pro Gly Leu Ser Glu
 225 230 235 240
 Phe Leu Glu Lys Met Ala Glu Lys Tyr Glu Met His Ile Tyr Thr Met
 245 250 255
 Ala Thr Arg Asn Tyr Ala Leu Ser Ile Ala Lys Ile Ile Asp Pro Asp
 260 265 270
 Gly Lys Tyr Phe Gly Asp Arg Ile Leu Ser Arg Asp Glu Ser Gly Ser
 275 280 285
 Leu Thr His Lys Asn Leu Lys Arg Leu Phe Pro Val Asp Gln Ser Met
 290 295 300
 Val Val Ile Ile Asp Asp Arg Gly Asp Val Trp Gln Trp Glu Ser Asn
 305 310 315 320
 Leu Ile Lys Val Val Pro Tyr Asp Phe Phe Val Gly Ile Gly Asp Ile
 325 330 335
 Asn Ser Ser Phe Leu Pro Lys Lys Asn Gly Gln Leu Thr Gly Pro Thr
 340 345 350
 Lys Lys Arg Lys Ser Ile Ala Lys Leu Glu Ala Ala Ala Glu Leu Ala
 355 360 365
 Lys Glu Ser Asp Thr Asn Asn Asp Lys Gln Glu Thr Glu Ser Gly Glu
 370 375 380
 Glu Glu Gly Glu Glu Asp Ala Asp Gly His Ser Asp Val Ser Asn Ser
 385 390 395 400
 Pro Val Glu Arg Ile Leu Glu Leu Gly Gly Glu Gly Asn Thr Ser
 405 410 415
 Leu Leu Leu Glu Gln Ser Leu Thr Arg Asn Gln Ser Ile Glu Glu Gln
 420 425 430
 Gln Gln Lys Arg Pro Leu Ala Lys Leu Gln His Asp Leu Glu Gln Met
 435 440 445
 His Glu His Arg His Asp Ser Asp Ser Lys Ser Glu Ser Gly Ser Asp
 450 455 460
 Asp Glu Ser Asp Glu Glu Asp Asn Leu Leu Phe Asp Asp Asp Asn Glu
 465 470 475 480
 Leu Ala Ala Leu Asp Lys Val Leu Gly Asn Ile His Gln Gly Tyr Tyr
 485 490 495

Asn Leu Phe Asp Lys Asp Lys Ile Asn Lys Pro Asp Leu Thr Glu Ile
 500 505 510
 Ile Pro Ser Met Lys Ser Lys Thr Leu Glu Gly Ile Thr Val Leu Phe
 515 520 525
 Ser Gly Ile Ile Pro Leu Gly Ile Asn Leu Asp Ser Ala Asp Ile Val
 530 535 540
 Ile Trp Cys Arg Gln Phe Gly Val Lys Val Val Asn Glu Val Tyr Pro
 545 550 555 560
 Glu Val Thr His Val Val Cys Arg Asp Val Ser Glu Gly Ala Gly Pro
 565 570 575
 Thr Phe Lys Thr Arg Val Ala Arg Lys Leu Tyr Pro Asp Thr Ile Lys
 580 585 590
 Ile Val Asn Pro Asp Trp Leu Phe Ala Cys Leu Ser Asn Trp Thr Lys
 595 600 605
 Val Asp Glu Lys Asp Tyr Leu Ile Ser Thr Asp Asp Thr Lys Leu Trp
 610 615 620
 Thr Val Lys Glu Asn Glu Ile Thr Lys Tyr Gln Lys Ala Leu Glu Asp
 625 630 635 640
 Arg Ser Ala Leu Ala Asn Ala Thr His Ile Asp Ser Ile Glu Ser Phe
 645 650 655
 Asp Glu Tyr Asp Leu Asp Glu Ala Asn Gln Glu Val Asp Asp Phe Leu
 660 665 670
 Ala Gly Leu Ser Asp Asp Asp Glu Glu Glu Glu Glu Glu Glu Asp
 675 680 685
 Glu Glu Ile Glu Asn Pro Glu Ser Asn Asn Asp Asp Glu Glu Ile Tyr
 690 695 700
 Glu Gln Ser Thr Asn Gly His Asp Ser Phe Ile Lys Asp Ala Tyr Ser
 705 710 715 720
 Lys Lys Arg Asn Arg Asp Glu Glu Glu Val Gln Leu Val Lys Lys Gln
 725 730 735
 Lys Ile Glu Asn Gly Glu Asn Gly Glu Asn Glu Asn Glu Asn Asp Leu
 740 745 750
 Asp Asp Leu Glu Lys Glu Leu Leu Asp Gly Phe Asp Asp Leu Glu Glu
 755 760 765

<210> 106

<211> 1042

<212> PRT

<213> Candida albicans

<400> 106

Met Gly Lys Lys Ala Ile Asp Ala Arg Ile Pro Ala Leu Ile Arg Asn
 1 5 10 15
 Gly Val Gln Glu Lys Gln Arg Ser Phe Phe Ile Ile Val Gly Asp Lys
 20 25 30
 Ala Arg Asn Gln Leu Pro Asn Leu His Tyr Leu Met Met Ser Ala Asp
 35 40 45
 Leu Lys Met Asn Lys Ser Val Leu Trp Ala Tyr Lys Lys Lys Leu Leu
 50 55 60
 Gly Phe Thr Ser His Arg Gln Lys Arg Glu Ala Lys Ile Lys Lys Asp
 65 70 75 80
 Ile Lys Arg Gly Ile Arg Glu Val Asn Glu Gln Asp Pro Phe Glu Ala
 85 90 95
 Phe Ile Ser Asn Gln His Ile Arg Tyr Val Tyr Tyr Lys Glu Thr Glu
 100 105 110
 Lys Ile Leu Gly Asn Thr Tyr Gly Met Cys Ile Leu Gln Asp Phe Glu
 115 120 125

Ala Ile Thr Pro Asn Leu Leu Ala Arg Thr Ile Glu Thr Val Glu Gly
 130 135 140
 Gly Gly Leu Val Val Ile Leu Leu Lys Asn Met Thr Ser Leu Lys Gln
 145 150 155 160
 Leu Tyr Thr Met Ser Met Asp Ile His Ser Arg Tyr Arg Thr Glu Ala
 165 170 175
 His Asp Asp Val Val Ala Arg Phe Asn Glu Arg Phe Leu Leu Ser Leu
 180 185 190
 Gly Ser Cys Glu Asn Cys Leu Val Asp Asp Glu Leu Asn Val Leu
 195 200 205
 Pro Ile Ser Gly Gly Lys His Val Lys Pro Leu Pro Pro Lys Asp Asp
 210 215 220
 Asp Glu Leu Thr Pro Asn Ala Lys Glu Leu Lys Glu Leu Lys Glu Ser
 225 230 235 240
 Leu Ala Asp Val Gln Pro Ala Gly Ser Leu Val Ala Leu Ser Lys Thr
 245 250 255
 Ile Asn Gln Ala Gln Ala Ile Leu Thr Phe Ile Asp Val Ile Ser Glu
 260 265 270
 Lys Thr Leu Arg Asn Thr Val Thr Leu Thr Ala Gly Arg Gly Arg Gly
 275 280 285
 Lys Ser Ala Ala Leu Gly Ile Ala Ile Ala Ala Ile Ser His Gly
 290 295 300
 Tyr Ser Asn Ile Phe Val Thr Ser Pro Ser Pro Glu Asn Leu Lys Thr
 305 310 315 320
 Leu Phe Glu Phe Ile Phe Lys Gly Phe Asp Ala Leu Gly Tyr Thr Glu
 325 330 335
 His Met Asp Tyr Asp Ile Ile Gln Ser Thr Asn Pro Ser Phe Asn Lys
 340 345 350
 Ala Ile Val Arg Val Asp Val Lys Arg Glu His Arg Gln Thr Ile Gln
 355 360 365
 Tyr Ile Ser Pro Asn Asp Ser His Val Leu Gly Gln Ala Glu Leu Leu
 370 375 380
 Ile Ile Asp Glu Ala Ala Ala Ile Pro Leu Pro Ile Val Lys Lys Leu
 385 390 395 400
 Met Gly Pro Tyr Leu Ile Phe Met Ala Ser Thr Ile Asn Gly Tyr Glu
 405 410 415
 Gly Thr Gly Arg Ser Leu Ser Leu Lys Leu Ile Gln Gln Leu Arg Thr
 420 425 430
 Gln Ser Asn Asn Ala Thr Pro Ser Glu Thr Thr Val Val Ser Arg Asp
 435 440 445
 Lys Lys Ser Asn Glu Ile Thr Gly Ala Leu Thr Arg Thr Leu Lys Glu
 450 455 460
 Val Val Leu Asp Glu Pro Ile Arg Tyr Ala Pro Gly Asp Pro Ile Glu
 465 470 475 480
 Lys Trp Leu Asn Lys Leu Leu Cys Leu Asp Val Ser Leu Ser Lys Asn
 485 490 495
 Ala Lys Phe Ala Thr Lys Gly Thr Pro His Pro Ser Gln Cys Gln Leu
 500 505 510
 Phe Tyr Val Asn Arg Asp Thr Leu Phe Ser Tyr His Pro Val Ser Glu
 515 520 525
 Ala Phe Leu Gln Lys Met Met Ala Leu Tyr Val Ala Ser His Tyr Lys
 530 535 540
 Asn Ser Pro Asn Asp Leu Gln Leu Met Ser Asp Ala Pro Ala His Gln
 545 550 555 560
 Leu Phe Val Leu Leu Pro Pro Ile Glu Ala Gly Asp Asn Arg Val Pro
 565 570 575
 Asp Pro Leu Cys Val Ile Gln Leu Ala Leu Glu Gly Glu Ile Ser Lys
 580 585 590

Glu Ser Val Arg Lys Ser Leu Ser Arg Gly Gln Arg Ala Gly Gly Asp
 595 600 605
 Leu Ile Pro Trp Leu Ile Ser Gln Gln Phe Gln Asp Glu Glu Phe Ala
 610 615 620
 Ser Leu Ser Gly Ala Arg Val Val Arg Ile Ala Thr Asn Pro Glu Tyr
 625 630 635 640
 Ser Gly Met Gly Tyr Gly Ser Arg Ala Met Glu Leu Leu Arg Asp Tyr
 645 650 655
 Tyr Ser Gly Lys Phe Thr Asp Ile Ser Glu Ser Thr Glu Leu Asn Asp
 660 665 670
 His Thr Ile Thr Arg Val Thr Asp Ser Glu Leu Ala Asn Ala Ser Leu
 675 680 685
 Lys Asp Glu Ile Lys Leu Arg Asp Val Lys Thr Leu Pro Pro Leu Leu
 690 695 700
 Leu Lys Leu Ser Glu Lys Ala Pro Tyr Tyr Leu His Tyr Leu Gly Val
 705 710 715 720
 Ser Tyr Gly Phe Thr Ser Gln Leu His Lys Phe Trp Lys Lys Ala Gly
 725 730 735
 Phe Thr Pro Val Tyr Leu Arg Gln Thr Pro Asn Glu Leu Thr Gly Glu
 740 745 750
 His Thr Ser Val Val Ile Ser Val Leu Pro Gly Arg Glu Asp Lys Trp
 755 760 765
 Leu His Glu Phe Ser Lys Asp Phe His Lys Arg Phe Leu Ser Leu Leu
 770 775 780
 Ser Tyr Glu Phe Lys Lys Phe Gln Ala Ser Gln Ala Leu Ser Ile Ile
 785 790 795 800
 Glu Ala Ala Glu Gln Gly Glu Gly Asp Glu Thr Thr Ser Gln Lys Leu
 805 810 815
 Thr Lys Glu Gln Leu Asp Ser Leu Leu Ser Pro Phe Asp Leu Lys Arg
 820 825 830
 Leu Asp Ser Tyr Ala Asn Asn Leu Leu Asp Tyr His Val Ile Val Asp
 835 840 845
 Met Leu Pro Leu Ile Ser Gln Leu Phe Phe Ser Lys Lys Thr Gly Gln
 850 855 860
 Asp Ile Ser Leu Ser Ser Val Gln Ser Ala Ile Leu Leu Ala Ile Gly
 865 870 875 880
 Leu Gln His Lys Asp Met Asp Gln Ile Ala Lys Glu Leu Asn Leu Pro
 885 890 895
 Thr Asn Gln Ala Met Ala Met Phe Ala Lys Ile Ile Arg Lys Phe Ser
 900 905 910
 Thr Tyr Phe Arg Lys Val Leu Ser Lys Ala Ile Glu Glu Ser Met Pro
 915 920 925
 Asp Leu Glu Asp Glu Asn Val Asp Ala Met Asn Gly Lys Glu Thr Glu
 930 935 940
 Gln Ile Asp Tyr Lys Ala Ile Glu Gln Lys Leu Gln Asp Asp Leu Glu
 945 950 955 960
 Glu Ala Gly Asp Glu Ala Ile Lys Glu Met Arg Glu Lys Gln Arg Glu
 965 970 975
 Leu Ile Asn Ala Leu Asn Leu Asp Lys Tyr Ala Ile Ala Glu Asp Ala
 980 985 990
 Glu Trp Asp Glu Lys Ser Met Asp Lys Ala Thr Lys Gly Lys Gly Asn
 995 1000 1005
 Val Val Ser Ile Lys Ser Gly Lys Arg Lys Ser Lys Glu Asn Ala Asn
 1010 1015 1020
 Asp Ile Tyr Glu Lys Glu Met Lys Ala Val Lys Lys Ser Lys Lys Ser
 1025 1030 1035 1040
 Lys Lys

<210> 107
 <211> 127
 <212> PRT
 <213> Candida albicans

<400> 107
 Met Ala Ala Phe Asp Glu Ile Phe Asp Tyr Val Asp Arg Asp Thr Phe
 1 5 10 15
 Phe Gln Tyr Phe Arg Leu Thr Leu Val Val Cys Thr Tyr Leu Ile Phe
 20 25 30
 Arg Lys Tyr Tyr Ser Ser Trp Ala Ile Lys Lys Gln Thr Ala Thr Gln
 35 40 45
 Leu Glu Gln Asp Lys Arg Glu Gln Ser Glu Lys Ser Glu Arg Glu Ala
 50 55 60
 Lys Glu Ser Lys Glu Lys Phe Asp Thr Ile Ser Asn Glu Ala Lys Glu
 65 70 75 80
 Phe Gly Trp Gly Lys Lys Thr Arg Asn Asn Val Lys Leu Thr Glu Ala
 85 90 95
 Val Leu Ala Glu Tyr Ser Glu Gln Gln Arg Gln Arg Asn Gln Thr Ser
 100 105 110
 Tyr Asp Ala Gln Glu Asp Ala Asp Ile Asp Asp Leu Leu Glu Asp
 115 120 125

<210> 108
 <211> 289
 <212> PRT
 <213> Candida albicans

<400> 108
 Met Ser Phe Arg Gly Gly Gly Gly Ser Gly Gly Arg Ser Thr Gln Arg
 1 5 10 15
 Thr Ile Leu Pro Phe Gly Leu Asp Tyr Ala Asp Ile Ile Ser Ser Thr
 20 25 30
 Gln Glu Thr Glu Lys Pro Gln Leu Leu Leu Pro Ile Asn Gly Asp Ile
 35 40 45
 Thr Glu Ile Glu Ser Ile Ile Ala Lys Gln Ser Met Asn Phe Thr Lys
 50 55 60
 Leu Met Ser Glu Gly Pro Phe Phe Thr Gly Asn Leu Asp Ser Ile Glu
 65 70 75 80
 Ile Thr Lys Lys Arg Asn His Asn Asp Ser Glu Asn Glu Glu Glu Glu
 85 90 95
 Glu Glu Glu Gly Gly Asp Thr Glu Asn Thr Gly Asp Arg Lys Lys Lys
 100 105 110
 Lys Ser Lys Thr Asn Gly Asp Gly Ser Ser Ser Gly Ser Gly Ser Gly
 115 120 125
 Ser Ala Ser Gly Asp Gly Ile Glu Arg Tyr Ser Asp Arg Tyr Lys Lys
 130 135 140
 Ile Gln Lys Ile Gly Arg Thr Ile Asp Glu His Pro Tyr Gln Pro Glu
 145 150 155 160
 Tyr Phe Pro Ser Glu Leu Tyr Ser Val Met Gly Ile Thr Asn Lys His
 165 170 175
 Asp Lys Lys Lys Phe Leu Leu Leu Ser Lys Phe Lys Ser Asn Gly Gly
 180 185 190
 Leu Lys Gln Ile Leu Ser Asn Glu Lys Leu Glu Asn Leu Asp Glu Gln
 195 200 205
 Ser Lys Leu Asn Ser Met Lys Glu Lys Met Leu Ser Met Ile Asp Asn
 210 215 220

Ser Val Asn Val Asn Asp Asp Asp Asn Asn Asn Asp Gly Lys Thr Arg
 225 230 235 240
 Ser Gly Asp Glu Gln Glu Ile Asp Glu Asp Asp Leu Asp Asp Glu Phe
 245 250 255
 Glu Asp Glu Asp Asp Asp Tyr Asn Ala Glu Lys Tyr Phe Asp Asp
 260 265 270
 Gly Asp Asp Asp Asp Gly Gly Asp Asp Gly Gly Asp Asp Glu Ala Ala
 275 280 285
 Phe

<210> 109

<211> 507

<212> PRT

<213> Candida albicans

<400> 109

Met Leu Ala Ser Lys Lys Lys Arg Thr Arg Arg Ile Lys Arg Gln Pro
 1 5 10 15
 Ile Cys Glu Gln Ile Pro Thr Ser Asn Thr Ala Phe Phe Phe Thr Leu
 20 25 30
 Asp Ile Pro Ile Met Pro Val Asn Phe Leu Thr Ser Val Val Phe Asp
 35 40 45
 Gly Pro Glu Val Ile Pro Tyr Trp Asp Gln Ile Lys Glu Tyr Gly Pro
 50 55 60
 Thr Val Leu Pro Ile Leu Leu Thr Leu Ala Gly Ala Lys Tyr Tyr Phe
 65 70 75 80
 His Gly Ala Thr Asn Thr Trp Glu Arg Asp Met His Gly Lys Val Phe
 85 90 95
 Met Ile Thr Gly Gly Thr Ser Gly Ile Gly Ala Gln Ile Ala Tyr Glu
 100 105 110
 Leu Gly Gln Arg Gly Ala Gln Leu Ile Leu Leu Thr Arg Arg Thr Asn
 115 120 125
 Asp Gln Trp Val Ala Glu Tyr Ile Glu Asp Leu Arg Asp Lys Thr Asn
 130 135 140
 Asn Gly Leu Ile Tyr Ala Glu Glu Cys Asp Leu Ser Ser Leu Tyr Ser
 145 150 155 160
 Ile Arg Lys Phe Ala Thr Arg Trp Leu Asp Asn Gln Pro Pro Arg Arg
 165 170 175
 Leu Asp Gly Val Ile Cys Cys Ala Ala Glu Cys Ile Pro Arg Gly Lys
 180 185 190
 Ser Arg Gln Ile Thr Met Asp Gly Val Glu Arg Gln Ile Gly Ile Asn
 195 200 205
 Tyr Leu Ala His Phe His Leu Leu Thr Leu Leu Gly Pro Ser Leu Arg
 210 215 220
 Val Gln Pro Pro Asp Arg Asn Val Arg Val Leu Ile Ala Thr Cys Ser
 225 230 235 240
 Ser Gln Asn Leu Gly Asp Val Asp Leu Asn Asp Leu Leu Trp Ser Asn
 245 250 255
 Lys Arg Tyr Pro Ala Thr Gln Pro Trp Lys Val Tyr Gly Thr Ser Lys
 260 265 270
 Leu Leu Leu Gly Leu Phe Ala Lys Glu Tyr Gln Arg Gln Leu Met Gly
 275 280 285
 Tyr Glu Arg Lys Asp Lys Ala Pro Cys Asn Val Arg Ile Asn Leu Ile
 290 295 300
 Asn Pro Gly Ile Val Arg Thr Pro Ser Thr Arg Arg Phe Leu Ser Leu
 305 310 315 320

Gly	Thr	Val	Trp	Gly	Leu	Ile	Ile	Tyr	Leu	Ile	Leu	Phe	Pro	Ile	Trp
				325					330					335	
Trp	Leu	Phe	Phe	Lys	Ser	Ala	Glu	Gln	Gly	Ala	Gln	Ser	Phe	Tyr	Phe
			340					345					350		
Ala	Leu	Phe	Ala	Pro	Ile	Phe	Met	Lys	Ile	Glu	Gly	Gly	Asn	Val	Val
		355					360				365				
Gln	Glu	Cys	Lys	Ile	Met	Thr	Lys	Val	Arg	Lys	Glu	Tyr	Thr	Asp	Asp
	370					375				380					
Asp	Leu	Gln	Gln	Lys	Val	Phe	His	Asn	Thr	Glu	Glu	Leu	Ile	Lys	Gln
385				390					395					400	
Ile	Glu	Thr	Lys	Ser	Ala	Ile	Glu	Arg	Lys	Lys	His	Glu	Asn	Ala	Lys
			405					410					415		
Lys	Thr	Pro	Glu	Gln	Lys	Ala	Lys	Glu	Arg	Gln	Glu	Glu	Leu	Asn	Arg
			420					425					430		
Lys	Arg	Asp	Leu	His	Ile	Lys	Pro	Glu	Thr	Pro	Glu	Glu	Leu	Glu	Ser
	435					440				445					
Lys	Leu	Asn	Ser	Leu	Arg	Asn	Gln	Ile	Gly	Met	Gly	Thr	Gly	Ile	Ser
	450					455			460						
Ser	Asn	Glu	Met	Pro	Leu	Phe	Pro	Asp	Asp	Glu	Thr	Leu	Lys	Lys	Val
465				470				475					480		
Ile	Ser	Ser	Lys	Lys	Asn	Ala	Ser	Ser	Asn	Asn	Ser	Gly	Gly	Ser	Lys
			485					490					495		
Ser	Asn	Lys	Ser	Gln	Lys	Lys	Ser	Lys	Lys	Val					
			500					505							

$\langle 210 \rangle$ 110

<211> 330

<212> PRT

<213> Candida albicans

$\langle 400 \rangle$ 110

Met	Thr	Asp	Met	Ser	Asn	Thr	Thr	Thr	Asp	Gly	Asn	Val	Ser	Ser	Ile
1				5					10					15	
Val	Val	Pro	Gly	Gln	Tyr	Ile	Ser	Pro	Thr	Tyr	Lys	Leu	Glu	Asn	Ser
			20					25					30		
Asn	Asn	Asp	Ser	Ser	Ile	Pro	Val	Lys	Tyr	Ile	Pro	Gly	Ser	Gly	Thr
		35				40					45				
Ile	Ile	Ser	Asn	Ile	Asn	Ile	Pro	Ser	Pro	Asn	Thr	Ser	Thr	Asn	Ser
	50					55				60					
Val	Lys	Ser	Met	Pro	Ile	Ile	Val	Ser	Thr	Ile	Leu	Gly	Asn	Val	Ser
65				70						75				80	
Ile	Ser	Pro	Ile	Asp	Gln	Thr	Pro	Thr	Ser	Lys	Pro	Ser	Asn	Asn	Asp
				85					90					95	
Asp	Met	Val	Ile	Asp	Asn	Glu	Gln	Thr	Lys	Ser	Asp	Glu	Asp	Lys	Asp
			100					105					110		
Lys	Asp	Lys	Tyr	Val	Lys	Ser	Tyr	Leu	Val	Ser	Val	Ile	Pro	Lys	Ser
		115					120					125			
Thr	Lys	His	Gln	Ser	Thr	Thr	Ser	Thr	Thr	Thr	Ser	Asn	Gln	Ser	Gly
	130					135					140				
Ser	Lys	Ala	Ile	Ser	Ala	Ile	Ala	Leu	Pro	Lys	Glu	Asn	Asp	Ile	Val
145					150					155				160	
Leu	Val	Arg	Ile	Thr	Lys	Ile	Thr	Lys	Ile	Gln	Ala	Tyr	Cys	Glu	Ile
				165					170					175	
Ile	Ser	Leu	Asp	Thr	Thr	Thr	Asn	Ile	Leu	Pro	Asp	Ser	Gly	Leu	Gly
			180					185					190		
Asn	Asn	Gly	Asn	Gly	Ser	His	Val	Ser	Met	Ser	Ile	Thr	Gly	Ser	Asn
		195				200						205			

Ser Gln His Asn Phe Asn Gln Asn Ser Ile Ala Ser Ser Gln Ser Thr
 210 215 220
 Asn Gln Ser Val Gln Ile Tyr Glu Leu Gly Glu Asn Phe Lys Gly Ile
 225 230 235 240
 Ile Arg Ile Asn Asp Ile Arg Ser Thr Glu Arg Asp Lys Leu Lys Leu
 245 250 255
 Ile Asp Cys Phe Lys Pro Gly Asp Ile Val Lys Ala Gln Val Ile Ser
 260 265 270
 Leu Gly Asp Gly Ser Asn Tyr Tyr Leu Thr Thr Ala Lys Asn Glu Leu
 275 280 285
 Gly Val Val Phe Ala Lys Ser Glu Asn Gly Ala Gly Asp Leu Met Tyr
 290 295 300
 Pro Ile Asp Trp Gln Asn Met Ile Asp Ile Asn Ser Gly Val Ile Glu
 305 310 315 320
 Lys Arg Lys Asn Ala Asn Pro Phe Leu Gln
 325 330

<210> 111
 <211> 221
 <212> PRT
 <213> Candida albicans

<400> 111
 Met Ala Gly Asp Leu Asn Leu Lys Lys Ser Trp Asn Pro Ala Leu Val
 1 5 10 15
 Lys Asn Gln Gln Lys Val Trp Glu Glu Glu Gln Gln Lys Leu Asp Glu
 20 25 30
 Leu Lys Arg Ile Lys Glu Arg Asn Gln Glu Tyr Lys Gln Glu Gln Glu
 35 40 45
 Tyr Leu Glu Leu Leu Lys Leu Gln His Gly Asp Gln Phe Gln Ile Lys
 50 55 60
 Asp Leu Asn Lys Gln Gln Lys Leu Lys Ile Ser Lys Leu Asn Trp Met
 65 70 75 80
 Tyr Asp Asp Val Pro Phe Glu Gly Asn Glu Lys Val Glu Glu Asn Ser
 85 90 95
 Ser Gly Phe Ile Glu Ser Asn Val Glu Phe Thr Asp Gly Lys Ser Lys
 100 105 110
 Val Glu Asn Leu Leu Lys Gly Asn His Val Val Gly Lys Lys Arg Asp
 115 120 125
 Gly Ser Gly Thr Ser Asp Arg Ile Asn Lys Ile Ile Gly Val Gly Met
 130 135 140
 Thr Lys Ser Ser Lys Val Ser Tyr Ser Asp Asp Pro Leu Leu Lys Ile
 145 150 155 160
 Lys Gln Gln Gln Gln Ala Gln Arg Val Ala Arg Lys Gln His Pro
 165 170 175
 Ser Asp Lys His Ser His Arg Phe Arg His Ser Ser Lys Ser Ser Ser
 180 185 190
 Asp Arg Val His Lys Ser His Glu His Glu Arg Ser Arg Lys His Asn
 195 200 205
 Ser Ser His Thr Arg His Lys Asp Gly Ser Pro His Arg
 210 215 220

<210> 112
 <211> 778
 <212> PRT
 <213> Candida albicans

<400> 112

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Met Leu Lys Asn Asp Thr Val Phe Thr Lys Asp Ile Ser Cys Thr Ala
 1           5           10           15
Ile Thr Gly Lys Asp Ala Trp Asn Pro Thr Pro Gln Pro Ile Thr Ile
          20           25           30
Ser Leu Ser Phe Thr Asp Phe Lys Ala Ser Glu Leu Asp Asn Leu Lys
          35           40           45
Ser Ile Asn Tyr Ala Val Ile Thr Arg Asn Val Thr Glu Phe Met Lys
          50           55           60
Ser Asn Glu His Leu Asn Phe Lys Ser Leu Gly Asn Ile Ala Gln Ala
65           70           75           80
Ile Ser Asp Ile Gly Leu Asp Gln Ser Arg Gly Gly Gly Ser Ile Val
          85           90           95
Asp Val Thr Ile Lys Ser Leu Lys Ser Glu Ile Arg Ala Glu Ser Val
          100          105          110
Glu Tyr Lys Ile Asn Arg Asn Thr Leu Gly Gln Pro Val Pro Leu Asp
          115          120          125
Ile Phe Gln Val Asn Lys Leu Arg Leu Leu Ile Ile Val Phe Thr Phe
          130          135          140
Glu Arg Leu Gln Lys Gln Ile Val Asp Val Asp Gln Phe Lys Ile Pro
145          150          155          160
Asn Ser Asn Leu Tyr Phe His Gln Ile Ile Ala Asp Ile Val Ser Tyr
          165          170          175
Val Glu Ser Ser Asn Phe Lys Thr Val Glu Ala Leu Val Ser Lys Ile
          180          185          190
Gly Gln Leu Thr Phe Gln Lys Tyr Asp Gly Val Ala Glu Val Val Ala
          195          200          205
Thr Val Thr Lys Pro Asn Ala Ser His Val Glu Gly Val Gly Val Ser
          210          215          220
Ser Thr Met Val Lys Asn Phe Lys Asp Met Glu Pro Val Lys Phe Glu
225          230          235          240
Asn Thr Ile Ala Gln Thr Asn Arg Ala Phe Asn Leu Pro Val Glu Asn
          245          250          255
Glu Lys Thr Glu Asp Tyr Thr Gly Tyr His Thr Ala Phe Ile Ala Phe
          260          265          270
Gly Ser Asn Thr Gly Asn Gln Val Glu Asn Ile Thr Asn Ser Phe Glu
          275          280          285
Leu Leu Gln Lys Tyr Gly Ile Thr Ile Glu Ala Thr Ser Ser Leu Tyr
          290          295          300
Ile Ser Lys Pro Met Tyr Tyr Leu Asp Gln Pro Asp Phe Phe Asn Gly
305          310          315          320
Val Ile Lys Val Asn Phe Gln Asn Ile Ser Pro Phe Gln Leu Leu Lys
          325          330          335
Ile Leu Lys Asp Ile Glu Tyr Lys His Leu Glu Arg Lys Lys Asp Phe
          340          345          350
Asp Asn Gly Pro Arg Ser Ile Asp Leu Asp Ile Ile Leu Tyr Asp Asp
          355          360          365
Leu Gln Leu Asn Thr Glu Asn Leu Ile Ile Pro His Lys Ser Met Leu
          370          375          380
Glu Arg Thr Phe Val Leu Gln Pro Leu Cys Glu Val Leu Pro Pro Asp
385          390          395          400
Tyr Ile His Pro Ile Ser Ala Glu Ser Leu His Ser His Leu Gln Gln
          405          410          415
Leu Ile Asn Asp Lys Pro Gln Glu Thr Val Gln Glu Ser Ser Asp Leu
          420          425          430
Leu Gln Phe Ile Pro Val Ser Arg Leu Pro Val Lys Asp Asn Ile Leu
          435          440          445
Lys Phe Asp Gln Ile Asn His Lys Ser Pro Thr Leu Ile Met Gly Ile
          450          455          460

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Leu Asn Met Thr Pro Asp Ser Phe Ser Asp Gly Gly Lys His Phe Gly
 465 470 475 480
 Lys Glu Leu Asp Asn Thr Val Lys Gln Ala Glu Lys Leu Val Ser Glu
 485 490 495
 Gly Ala Thr Ile Ile Asp Ile Gly Gly Val Ser Thr Arg Pro Gly Ser
 500 505 510
 Val Glu Pro Thr Glu Glu Glu Glu Leu Glu Arg Val Ile Pro Leu Ile
 515 520 525
 Lys Ala Ile Arg Gln Ser Ser Asn Pro Asp Leu Ser Lys Val Leu Ile
 530 535 540
 Ser Val Asp Thr Tyr Arg Arg Asn Val Ala Glu Gln Ser Leu Leu Val
 545 550 555 560
 Gly Ala Asp Ile Ile Asn Asp Ile Ser Met Gly Lys Tyr Asp Glu Lys
 565 570 575
 Ile Phe Asp Val Val Ala Lys Tyr Gly Cys Pro Tyr Ile Met Asn His
 580 585 590
 Thr Arg Gly Ser Pro Lys Thr Met Ser Lys Leu Thr Asn Tyr Glu Ser
 595 600 605
 Asn Thr Asn Asp Asp Ile Ile Glu Tyr Ile Ile Asp Pro Lys Leu Gly
 610 615 620
 His Gln Glu Leu Asp Leu Ser Pro Glu Ile Lys Asn Leu Leu Asn Gly
 625 630 635 640
 Ile Ser Arg Glu Leu Ser Leu Gln Met Phe Lys Ala Met Ala Lys Gly
 645 650 655
 Val Lys Lys Trp Gln Ile Ile Leu Asp Pro Gly Ile Gly Phe Ala Lys
 660 665 670
 Asn Leu Asn Gln Asn Leu Ala Val Ile Arg Asn Ala Ser Phe Phe Lys
 675 680 685
 Lys Tyr Ser Ile Gln Ile Asn Glu Arg Val Asp Asp Val Thr Ile Lys
 690 695 700
 His Lys Tyr Leu Ser Phe Asn Gly Ala Cys Val Leu Val Gly Thr Ser
 705 710 715 720
 Arg Lys Lys Phe Leu Gly Thr Leu Thr Gly Asn Glu Val Pro Ser Asp
 725 730 735
 Arg Val Phe Gly Thr Gly Ala Thr Val Ser Ala Cys Ile Glu Gln Asn
 740 745 750
 Thr Asp Ile Val Arg Val His Asp Val Lys Glu Met Lys Asp Val Val
 755 760 765
 Cys Ile Ser Asp Ala Ile Tyr Lys Asn Val
 770 775

<210> 113
 <211> 148
 <212> PRT
 <213> Candida albicans

<400> 113
 Met Ser Asp Ile Asp Ile Asp Asn Val Leu Asn Leu Glu Glu Glu Gln
 1 5 10 15
 Tyr Glu Leu Gly Phe Lys Glu Gly Gln Ile Gln Gly Thr Lys Asp Gln
 20 25 30
 Tyr Leu Glu Gly Lys Glu Tyr Gly Tyr Gln Thr Gly Phe Gln Arg Phe
 35 40 45
 Leu Ile Ile Gly Tyr Ile Gln Glu Leu Met Lys Phe Trp Leu Ser His
 50 55 60
 Ile Asp Gln Tyr Asn Asn Ser Ser Ser Leu Arg Asn His Leu Asn Asn
 65 70 75 80

Leu Glu Asn Ile Leu Ala Gln Ile Ser Ile Thr Asn Gly Asp Lys Glu
 85 90 95
 Val Glu Asp Tyr Glu Lys Asn Ile Lys Lys Ala Arg Asn Lys Leu Arg
 100 105 110
 Val Ile Ala Ser Ile Thr Lys Glu Thr Trp Lys Ile Asp Ser Leu Asp
 115 120 125
 Asn Leu Val Lys Glu Val Gly Gly Thr Leu Gln Val Ser Glu Asn Pro
 130 135 140
 Asp Asp Met Trp
 145

<210> 114
 <211> 269
 <212> PRT
 <213> Candida albicans

<400> 114
 Met Arg Gln Lys Arg Ala Lys Ala Tyr Lys Lys Gln Met Ser Val Tyr
 1 5 10 15
 Val His Ala Phe Lys Phe Arg Glu Pro Tyr Gln Ile Ile Val Asp Asn
 20 25 30
 Glu Leu Ile Thr Thr Cys Gln Ser Ala Ser Phe Asp Ile Asn Lys Gly
 35 40 45
 Phe Thr Arg Thr Ile Gln Ala Glu Asn Lys Pro Met Ile Thr Gln Cys
 50 55 60
 Cys Ile Gln Ala Leu Tyr Asp Thr Lys Asn Gln Pro Ala Ile Asp Ile
 65 70 75 80
 Ala Lys Ser Phe Glu Arg Arg Lys Cys Asn His Arg Glu Ala Ile Asp
 85 90 95
 Pro Ser Gln Cys Ile Glu Ser Ile Val Asn Ile Lys Gly Gln Asn Lys
 100 105 110
 His Arg Tyr Ile Val Ala Ser Gln Asp Leu Gln Leu Arg Lys Lys Leu
 115 120 125
 Arg Lys Ile Pro Gly Val Pro Leu Ile Tyr Met Asn Arg Ser Val Met
 130 135 140
 Val Met Glu Pro Ile Ser Asp Val Ser Asn Gln Tyr Asn Met Asn Tyr
 145 150 155 160
 Glu Ser Lys Lys Leu Thr Gly Gly Leu Asn Asp Ile Glu Ala Gly Lys
 165 170 175
 Leu Glu Lys Gln Asn Glu Gly Glu Asp Gly Asp Gly Asp Glu Ser Glu
 180 185 190
 Val Lys Lys Lys Lys Arg Lys Gly Pro Lys Glu Pro Asn Pro Leu Ser
 195 200 205
 Val Lys Lys Lys Lys Thr Asp Asn Ala Thr Ala Ala Ser Thr Asn Gln
 210 215 220
 Glu Gln Lys Lys Lys Pro Asn Arg Arg Lys Arg His Gly Lys Ser Lys
 225 230 235 240
 Ala Glu Glu Lys Glu Asp Gln Glu Gln Glu Val Asn Glu Ala Thr
 245 250 255
 Thr Asn Glu Asp Ala Gln Glu Ala Ile Thr Ala Thr Glu
 260 265

<210> 115
 <211> 306
 <212> PRT
 <213> Candida albicans

<400> 115

Met Thr Asp Leu Thr Pro Leu Phe Arg Gln Cys Val Asp Ile Val Gln
 1 5 10 15
 Gln Glu Tyr Lys Thr Gln Pro Thr Thr Ala Lys Gln Pro Tyr Tyr Leu
 20 25 30
 Asn Asp Thr Phe Ile Lys Glu Thr Thr Ala Phe Phe His Val Leu Thr
 35 40 45
 Asn Leu Asn Gln Phe Ile Asn Glu Thr Lys Ser Ser Tyr Leu Ala Ile
 50 55 60
 Asn Asp Asp Thr Lys Leu Ala Gly Ser Ile Asp Asp Lys Asn Lys Ile
 65 70 75 80
 Asp Glu Glu Phe Asn Tyr Lys Val Gln Gln Met Tyr Lys Arg Leu Asn
 85 90 95
 His Leu Glu Thr Tyr Glu Thr Lys Arg Gln Ser Leu Leu Pro Lys Thr
 100 105 110
 Ser Gly Trp Phe Ser Phe Leu Asp Glu Ser Asn Asp Gln Asp Ile Tyr
 115 120 125
 Phe Glu Thr Leu Ala Asn His Arg Met Gln Ile Leu Arg Phe Leu Met
 130 135 140
 Glu Thr Leu Asn His Val Asn Lys Arg Phe Glu Asn Ile Gln Gln Lys
 145 150 155 160
 Arg Leu Ala Arg Glu Arg Gln Leu Asn Leu Leu Asn Phe Gln Asn Phe
 165 170 175
 Glu Asp Gly Glu Glu Leu Glu Asp Val Phe Pro Thr Leu Asp Gln Ile
 180 185 190
 Gln Gln Val Pro Glu Leu Ser Gln Gln Gln Ile Gln Gln Leu Glu Thr
 195 200 205
 Glu Asn Gln Glu Phe Leu Asn Met Lys Thr Ser Gln Leu Lys Gln Val
 210 215 220
 Glu Lys Val Gln Gln Ser Ile Leu Asp Ile Val Asn Ile Gln Asn Glu
 225 230 235 240
 Leu Ala Phe Lys Leu Gln Asp Gln Gly Gln Gln Ile Glu Ser Leu Met
 245 250 255
 Asp Ser His Ala Asp Val Gln Thr Glu Val Gln Met Gly Asn Arg Thr
 260 265 270
 Leu Ser Gln Ala Thr Lys Lys Asn Lys Arg Gly Ala Asn Met Leu Val
 275 280 285
 Met Leu Cys Ile Val Leu Gly Val Leu Leu Val Leu Val Asp Tyr Val
 290 295 300
 Ser Phe
 305

<210> 116

<211> 192

<212> PRT

<213> Candida albicans

<400> 116

Met Ser Gly Ile Lys Ile Ser Leu Lys Lys Lys Asn Pro Lys Leu Lys
 1 5 10 15
 Lys Leu Ile Val Asn Asn Ser Gln Gln Thr Asp Glu Ser Ser Glu Gln
 20 25 30
 Gln Lys Lys Leu Ile Thr Ser Tyr Ser Thr Glu Asp Lys Thr Thr His
 35 40 45
 Lys Asp Glu Thr Lys Pro Ile Ile Val Leu Lys Gln Pro Cys Lys Ser
 50 55 60
 Met Leu Gln Lys Glu Ile Glu Ile Asp Glu Lys Pro Ile Leu Pro Tyr
 65 70 75 80

Gly Val Thr Thr Phe Glu Lys Val Glu Thr Thr Lys Gln Ser Met Ile
 85 90 95
 Lys Lys Ile Glu Ser Glu Asp Ser Asp Asp Asp Ser Ser Asp Asp Arg
 100 105 110
 Lys Ile Pro Ile Asp Glu Phe Gly Ala Ala Phe Leu Arg Gly Leu Gly
 115 120 125
 Trp Gln Glu Glu Glu Glu Lys Asn Lys Asp Asp Ser Lys Ser Thr Asn
 130 135 140
 Thr Gln Asn Leu Ser His Arg Lys His Gly Ile Thr Leu Gly Ile Gly
 145 150 155 160
 Ala Lys Pro Ile Asp Glu Glu Ile Ile Gln Asp Leu Asn Ser Thr Glu
 165 170 175
 Lys Gly Ile Pro Ile Ile Lys Arg Arg Lys Leu Asn His Ile Asn Lys
 180 185 190

<210> 117

<211> 714

<212> PRT

<213> Candida albicans

<400> 117

Met Ala Lys Ala Ser Lys Gln Thr Lys Lys Phe Gln Asn Lys His Leu
 1 5 10 15
 Lys His Thr Ile Glu Gln Arg Lys Lys Val Gln Ala Gln Asn Lys Lys
 20 25 30
 Ile Ala Ser Arg Lys Lys Ser Gly Ser Ser Ser Ser Gly Glu Ser Asn
 35 40 45
 Ala Pro Lys Arg Ala Asp Gly Lys Ala Lys Glu Val Phe Glu Asp Met
 50 55 60
 Ser Val Asp Asp Phe Phe Gly Gly Gly Phe Glu Val Pro Lys Glu Lys
 65 70 75 80
 Asn Lys Asn Lys Asn Lys Gln Asp Thr Ile Glu Glu Asn Glu Glu Glu
 85 90 95
 Asp Ser Ser Ser Glu Glu Glu Asp Glu Glu Ala Met Lys Glu Asn Leu
 100 105 110
 Lys Lys Leu Glu Ala Asp Asp Pro Glu Phe Tyr Lys Tyr Leu Lys Asp
 115 120 125
 Asn Asp Asn Asp Leu Leu Asp Phe Glu Ala Val Asn Pro Leu Asp Ala
 130 135 140
 Ile Ser Asp Asp Glu Gly Asp Glu Asp Asp Asp Glu Glu Ile Glu Lys
 145 150 155 160
 Glu Val Pro Ser Asp Asp Asp Ser Glu Glu Glu Pro Thr Leu Gly Lys
 165 170 175
 Val Lys Gly Ser Lys Ile Glu Ile Thr Lys Ser Leu Val Lys Lys Trp
 180 185 190
 Asn Gln Gln Leu Asp Lys Pro Thr Pro Lys Ile Thr Arg Asn Ile Leu
 195 200 205
 Ile Ala Phe Lys Ala Ala Val Asn Ile His Asn Ser Asp Ser Glu Asp
 210 215 220
 Tyr Lys Phe Ser Ile Thr Asp Pro Lys Ala Phe Ser Glu Leu Met Leu
 225 230 235 240
 Leu Val Leu Lys Lys Val Pro Ile Ser Val Gln Lys Leu Val Lys Tyr
 245 250 255
 Lys Thr Asn Thr Gln Gly Val Arg Thr Ile Pro Gln Lys Asn Gln Tyr
 260 265 270
 Ala Thr Gln Ile Ala Ala Ile Leu Lys Ser His Ala Gly Ser Phe Ile
 275 280 285

Thr Leu Leu Asn Asp Ile Thr Asn Thr Glu Thr Ala Ala Leu Ile Leu
 290 295 300
 Ala Ser Ile Tyr Glu Val Phe Pro Phe Tyr Leu Ser His Arg Arg Leu
 305 310 315 320
 Leu Lys Gln Ile Leu Thr Ala Val Val Asn Val Trp Ser Ser Ser Ser
 325 330 335
 Asp Ile Asp Thr Gln Ile Ser Thr Phe Ala Phe Leu Asn Asn Val Ser
 340 345 350
 Arg Glu Tyr Pro Lys Ser Val Leu Glu Thr Val Leu Lys Leu Thr Tyr
 355 360 365
 Ser Ser Phe Leu Gln Asn Cys Arg Lys Thr Asn Val His Thr Met Ala
 370 375 380
 Gln Ile Asn Phe Cys Lys Asn Ser Ala Val Glu Leu Phe Gly Ile Asn
 385 390 395 400
 Glu Thr Leu Gly Tyr Gln Val Gly Phe Glu Tyr Val Arg Gln Leu Ala
 405 410 415
 Ile His Leu Arg Asn Ser Ile Asn Ala Thr Ser Asn Ala Lys Glu Gly
 420 425 430
 Tyr Lys Thr Ile Tyr Asn Trp Gln Tyr Cys His Ser Leu Asp Phe Trp
 435 440 445
 Ser Arg Val Leu Ser Gln His Cys Asn Pro Glu Lys Glu Leu Gln Asn
 450 455 460
 His Lys Ser Lys Glu Ser Pro Leu Arg Gln Leu Ile Tyr Pro Leu Val
 465 470 475 480
 Gln Val Thr Leu Gly Ala Ile Arg Leu Ile Pro Thr Ala Gln Phe Phe
 485 490 495
 Pro Leu Arg Phe Tyr Leu Ile Arg Ser Leu Ile Arg Leu Ser Gln Ser
 500 505 510
 Thr Gly Val Phe Ile Pro Leu Phe Pro Leu Ile Ser Glu Ile Leu Ser
 515 520 525
 Ser Thr Ala Met Thr Lys Ala Pro Lys Ala Ser Thr Leu Gln Ala Val
 530 535 540
 Asp Phe Glu His Asn Ile Lys Val Asn Gln Ala Tyr Leu Gly Thr Arg
 545 550 555 560
 Val Tyr Gln Asp Gly Leu Cys Glu Gln Phe Ile Glu Leu Ser Gly Glu
 565 570 575
 Phe Phe Gly Leu Tyr Ala Lys Ser Ile Ala Phe Pro Glu Leu Val Thr
 580 585 590
 Pro Ala Val Leu Ala Leu Arg Arg Phe Val Lys Lys Ser Lys Asn Val
 595 600 605
 Lys Phe Asn Lys Gln Leu Gln Gln Leu Ile Glu Lys Leu Asn Ala Asn
 610 615 620
 Ala Val Phe Ile Thr Gly Lys Arg Ser Asn Val Glu Tyr Gly Pro Ser
 625 630 635 640
 Asn Lys Ala Glu Val Gln Gln Phe Leu Ser Asp Phe Glu Trp Glu Lys
 645 650 655
 Thr Pro Leu Gly Gln Tyr Val Ser Val Gln Arg Gln Leu Lys Ala Glu
 660 665 670
 Arg Leu Arg Ile Leu Lys Glu Ala Gln Glu Glu Glu Ala Lys Ala Gln
 675 680 685
 Ala Glu Gln Lys Lys Lys Glu Glu Glu Glu Asp Glu Gln Glu Asp Glu
 690 695 700
 Asp Ile Val Met Glu Glu Asp Asp Glu
 705 710

<210> 118

<211> 281

<212> PRT

<213> Candida albicans

<400> 118

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Met Ser Arg Gly Lys Thr Ile Arg Pro Ser Tyr Tyr Asp Glu Glu Glu
 1           5           10           15
Ser Ser Gln Asp Glu Leu Ser His Thr Leu Ser Lys Gly Arg Ser Asn
          20           25           30
Ile Gly Ser Gln Ser Asp Asp Glu Glu Met Ser Lys Ile Ser Phe Gly
 35           40           45
Ala Leu Asn Arg Ala Gln Ser Lys Leu Asn Lys His Asn Gln Lys His
 50           55           60
Lys Thr Gln Glu Asp Asn Tyr Lys Ser Ser Glu Glu Glu Phe Phe Asp
65           70           75           80
Ser Gly Ser Asp Ser Asp Gly Pro Pro Glu Glu Thr Ser Ser Lys Asp
          85           90           95
Thr Lys Lys Lys Lys Asn Lys His Ala Pro Ser Glu Ser Ser Ser Lys
          100           105           110
Arg Pro Val Ser Arg Ile Arg Asp Ile Pro Gly Leu Pro Ser Arg Lys
          115           120           125
Gln Gln Thr Leu His Thr Asp Ile Arg Phe Asp Ala Ala Tyr Gly Lys
          130           135           140
Ala Asp Leu Ala Lys Ala Arg Lys Asp Tyr Ala Phe Leu Asp Glu Tyr
145           150           155           160
Arg Lys Gln Glu Ile Ala Asn Met Glu Ser Leu Leu Lys Asp Lys Lys
          165           170           175
Ser Arg Leu Asn Asp Asp Glu Arg Glu Glu Ile Lys Leu Gln Leu Gln
          180           185           190
Ser Leu Lys Ser Arg Met Asp Thr Leu Lys Asn Arg Asp Leu Glu Asn
          195           200           205
Asn Ile Leu Ser Asn Tyr Lys Lys Gln Gln Met Glu Ser Phe Lys Glu
          210           215           220
Gly Lys Val Asn Lys Pro Tyr Phe Leu Lys Arg Ser Asp Lys Arg Lys
225           230           235           240
Ile Leu Gln Lys Ala Lys Phe Asp Ser Met Lys Pro Lys Gln Arg Glu
          245           250           255
Lys Ala Met Glu Arg Lys Arg Lys Lys Arg Leu Gly Lys Glu Phe Arg
          260           265           270
Gln Leu Glu Phe Lys Pro Thr Asn Arg
          275           280

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<210> 119

<211> 849

<212> PRT

<213> Candida albicans

<400> 119

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Met Ser Asp Gln Leu Glu Lys Asp Ile Glu Glu Ser Ile Ala Asn Leu
 1           5           10           15
Asp Tyr Gln Gln Asn Gln Glu His His Glu Thr Glu Gln Asp Lys Asp
          20           25           30
Lys Glu His Gln Asp Val Glu Lys Gln Ser Ser Glu Glu Glu Thr Lys
          35           40           45
Gly Ile Glu His Val Thr Asp Ser Asn Thr Asp Asp Ile Gly Val Thr
          50           55           60
Lys Ser Gln Asp Thr Glu Glu Val Ile Glu Asn Ser Pro Val Asp Pro
65           70           75           80
Gln Leu Lys Glu Gln Gln Glu Ser Thr Thr Lys Met Ser Leu Ser Glu
          85           90           95

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Arg Asp Leu Val Asp Glu Ile Asp Glu Leu Phe Thr Asn Ser Thr Lys
      100      105      110
Thr Val Thr Glu Asn Asn Gln Pro Ser Glu Thr Asn Lys Arg Ala Tyr
      115      120      125
Glu Ser Val Glu Thr Pro Gln Glu Leu Thr Pro Asn Asp Lys Arg Gln
      130      135      140
Lys Leu Asp Ala Asn Thr Glu Thr Ser Val Pro Thr Glu Leu Glu Ser
      145      150      155      160
Val Asn Asn His Asn Glu Gln Ser Gln Pro Ile Glu Pro Thr Gln Glu
      165      170      175
Arg Gln Pro Ser Thr Thr Glu Thr Thr Tyr Ser Ile Ser Val Pro Val
      180      185      190
Ser Thr Thr Asn Glu Val Glu Arg Ala Ser Ser Ser Ile Asn Glu Gln
      195      200      205
Glu Asp Leu Glu Met Ile Ala Lys Gln Tyr Gln Gln Ala Thr Asn Leu
      210      215      220
Glu Ile Glu Arg Ala Met Glu Gly His Gly Asp Gly Gly Gln His Phe
      225      230      235      240
Ser Thr Gln Glu Asn Gly Gln Pro Ser Gly Ser Ser Leu Ile Ser Ser
      245      250      255
Ile Val Pro Ser Asp Ser Glu Leu Leu Asn Thr Asn Gln Ala Tyr Ala
      260      265      270
Ala Tyr Thr Ser Leu Ser Ser Gln Leu Glu Gln His Thr Ser Ala Ser
      275      280      285
Ala Met Leu Ser Ser Ala Thr Leu Ser Ala Leu Pro Leu Ser Ile Ile
      290      295      300
Ala Pro Val Tyr Leu Pro Pro Arg Ile Gln Leu Leu Ile Asn Thr Leu
      305      310      315      320
Pro Thr Leu Asp Asn Leu Ala Thr Gln Leu Leu Arg Thr Val Ala Thr
      325      330      335
Ser Pro Tyr Gln Lys Ile Ile Asp Leu Ala Ser Asn Pro Asp Thr Ser
      340      345      350
Ala Gly Ala Thr Tyr Arg Asp Leu Thr Ser Leu Phe Glu Phe Thr Lys
      355      360      365
Arg Leu Tyr Ser Glu Asp Asp Pro Phe Leu Thr Val Glu His Ile Ala
      370      375      380
Pro Gly Met Trp Lys Glu Gly Glu Glu Thr Pro Ser Ile Phe Lys Pro
      385      390      395      400
Lys Gln Gln Ser Ile Glu Ser Thr Leu Arg Lys Val Asn Leu Ala Thr
      405      410      415
Phe Leu Ala Ala Thr Leu Gly Thr Met Glu Ile Gly Phe Phe Tyr Leu
      420      425      430
Asn Glu Ser Phe Leu Asp Val Phe Cys Pro Ser Asn Asn Leu Asp Pro
      435      440      445
Ser Asn Ala Leu Ser Asn Leu Gly Gly Tyr Gln Asn Gly Leu Gln Ser
      450      455      460
Thr Asp Ser Pro Val Gly Ala Arg Val Gly Lys Leu Leu Lys Pro Gln
      465      470      475      480
Ala Thr Leu Tyr Leu Asp Leu Lys Thr Gln Ala Tyr Ile Ser Ala Ile
      485      490      495
Glu Ala Gly Glu Arg Ser Lys Glu Glu Ile Leu Glu Asp Ile Leu Pro
      500      505      510
Asp Asp Leu His Val Tyr Leu Met Ser Arg Arg Asn Ala Lys Leu Leu
      515      520      525
Ser Pro Thr Glu Thr Asp Phe Val Trp Arg Cys Lys Gln Arg Lys Glu
      530      535      540
Ser Leu Leu Asn Tyr Thr Glu Glu Thr Pro Leu Ser Glu Gln Tyr Asp
      545      550      555      560

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<210> 120
<211> 1096
<212> PRT
<213> Candida albicans
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<400> 120																
Met	Ser	Gly	Pro	Val	Thr	Phe	Glu	Lys	Thr	Phe	Arg	Arg	Asp	Ala	Leu	
1				5					10					15		
Ile	Asp	Ile	Glu	Lys	Lys	Tyr	Gln	Lys	Val	Trp	Ala	Glu	Glu	Lys	Val	
			20					25					30			
Phe	Glu	Val	Asp	Ala	Pro	Thr	Phe	Glu	Glu	Cys	Pro	Ile	Glu	Asp	Val	
		35					40					45				
Glu	Gln	Val	Gln	Glu	Ala	His	Pro	Lys	Phe	Phe	Ala	Thr	Met	Ala	Tyr	
	50					55					60					
Pro	Tyr	Met	Asn	Gly	Val	Leu	His	Ala	Gly	His	Ala	Phe	Thr	Leu	Ser	
65					70					75					80	
Lys	Val	Glu	Phe	Ala	Thr	Gly	Phe	Gln	Arg	Met	Asn	Gly	Lys	Arg	Ala	
				85					90					95		
Leu	Phe	Pro	Leu	Gly	Phe	His	Cys	Thr	Gly	Met	Pro	Ile	Lys	Ala	Ala	

	100		105		110
Ala Asp Lys Ile Lys Arg Glu Val Glu Leu Phe Gly Ser Asp Phe Ser					
115		120		125	
Lys Ala Pro Ala Asp Asp Glu Asp Ala Glu Glu Ser Gln Gln Pro Ala					
130		135		140	
Lys Thr Glu Thr Lys Arg Glu Asp Val Thr Lys Phe Ser Ser Lys Lys					
145		150		155	160
Ser Lys Ala Ala Ala Lys Gln Gly Arg Ala Lys Phe Gln Tyr Glu Ile					
165		170		175	
Met Met Gln Leu Gly Ile Pro Arg Glu Glu Val Ala Lys Phe Ala Asn					
180		185		190	
Thr Asp Tyr Trp Leu Glu Phe Phe Pro Pro Leu Cys Gln Lys Asp Val					
195		200		205	
Thr Ala Phe Gly Ala Arg Val Asp Trp Arg Arg Ser Met Ile Thr Thr					
210		215		220	
Asp Ala Asn Pro Tyr Tyr Asp Ala Phe Val Arg Trp Gln Ile Asn Arg					
225		230		235	240
Leu Arg Asp Val Gly Lys Ile Lys Phe Gly Glu Arg Tyr Thr Ile Tyr					
245		250		255	
Ser Glu Lys Asp Gly Gln Ala Cys Leu Asp His Asp Arg Gln Ser Gly					
260		265		270	
Glu Gly Val Gly Pro Gln Glu Tyr Val Gly Ile Lys Ile Arg Leu Thr					
275		280		285	
Asp Val Ala Pro Gln Ala Gln Glu Leu Phe Lys Lys Glu Ser Leu Asp					
290		295		300	
Val Lys Glu Asn Lys Val Tyr Leu Val Ala Ala Thr Leu Arg Pro Glu					
305		310		315	320
Thr Met Tyr Gly Gln Thr Cys Cys Phe Val Ser Pro Lys Ile Asp Tyr					
325		330		335	
Gly Val Phe Asp Ala Gly Asn Gly Asp Tyr Phe Ile Thr Thr Glu Arg					
340		345		350	
Ala Phe Lys Asn Met Ser Phe Gln Asn Leu Thr Pro Lys Arg Gly Tyr					
355		360		365	
Tyr Lys Pro Leu Phe Thr Ile Asn Gly Lys Thr Leu Ile Gly Ser Arg					
370		375		380	
Ile Asp Ala Pro Tyr Ala Val Asn Lys Asn Leu Arg Val Leu Pro Met					
385		390		395	400
Glu Thr Val Leu Ala Thr Lys Gly Thr Gly Val Val Thr Cys Val Pro					
405		410		415	
Ser Asp Ser Pro Asp Asp Phe Val Thr Thr Arg Asp Leu Ala Asn Lys					
420		425		430	
Pro Glu Tyr Tyr Gly Ile Glu Lys Asp Trp Val Gln Thr Asp Ile Val					
435		440		445	
Pro Ile Val His Thr Glu Lys Tyr Gly Asp Lys Cys Ala Glu Phe Leu					
450		455		460	
Val Asn Asp Leu Lys Ile Gln Ser Pro Lys Asp Ser Val Gln Leu Ala					
465		470		475	480
Asn Ala Lys Glu Leu Ala Tyr Lys Glu Gly Phe Tyr Asn Gly Thr Met					
485		490		495	
Leu Ile Gly Lys Tyr Lys Gly Asp Lys Val Glu Asp Ala Lys Pro Lys					
500		505		510	
Val Lys Gln Asp Leu Ile Asp Glu Gly Leu Ala Phe Val Tyr Asn Glu					
515		520		525	
Pro Glu Ser Gln Val Ile Ser Arg Ser Gly Asp Asp Cys Cys Val Ser					
530		535		540	
Leu Glu Asp Gln Trp Tyr Ile Asp Tyr Gly Glu Glu Ala Trp Leu Gly					
545		550		555	560

109

Leu Ala Thr Glu Asp Ala Asp Thr Val Phe Asn Arg Lys Leu Thr Phe
 1010 1015 1020
 Asp Glu Ile Asp Thr Leu Lys Asn Val Val Glu Ile Val Lys Asn Ala
 1025 1030 1035 1040
 Pro Tyr Ser Leu Lys Val Glu Lys Leu Glu Ile Leu Ser Phe Asn Asn
 1045 1050 1055
 Gly Glu Thr Lys Gly Lys Asn Ile Ile Ser Gly Glu Asp Asn Ile Glu
 1060 1065 1070
 Leu Asn Phe Lys Gly Lys Ile Met Glu Asn Ala Val Pro Gly Glu Pro
 1075 1080 1085
 Gly Ile Phe Ile Lys Asn Val Glu
 1090 1095

<210> 121
 <211> 520
 <212> PRT
 <213> Candida albicans

<400> 121
 Met Asn Val Gly Ser Ile Leu Asn Asp Asp Pro Pro Ser Ser Gly Asn
 1 5 10 15
 Ala Asn Gly Asn Asp Asp Asn Thr Lys Ile Ile Lys Ser Pro Thr Ala
 20 25 30
 Tyr His Lys Pro Ser Val His Glu Arg His Ser Ile Thr Ser Met Leu
 35 40 45
 Asn Asp Thr Pro Ser Asp Ser Thr Pro Thr Lys Lys Pro Glu Pro Thr
 50 55 60
 Ile Ser Pro Glu Phe Arg Lys Pro Ser Ile Ser Ser Leu Thr Ser Pro
 65 70 75 80
 Ser Val Ala His Lys Pro Pro Pro Leu Pro Pro Ser Ser Ser Ser Val
 85 90 95

Gly Ser Ser Glu His Ser Ser Ala Arg Ser Ser Pro Ala Ile Thr Lys
 100 105 110
 Arg Asn Ser Ile Ala Asn Ile Ile Asp Ala Tyr Glu Glu Pro Ala Thr
 115 120 125
 Lys Thr Glu Lys Lys Ala Glu Leu Asn Ser Pro Lys Ile Asn Gln Ser
 130 135 140
 Thr Pro Val Pro Lys Leu Glu Glu His Glu Asn Asp Thr Asn Lys Val
 145 150 155 160
 Glu Lys Val Val Asp Ser Ala Pro Glu Pro Lys Pro Lys Lys Glu Pro
 165 170 175
 Gln Pro Val Phe Asp Asp Gln Asp Asp Leu Thr Lys Ile Lys Lys
 180 185 190
 Leu Lys Gln Ser Lys Lys Pro Arg Tyr Glu Thr Pro Pro Ile Trp
 195 200 205
 Ala Gln Arg Trp Val Pro Pro Asn Arg Gln Lys Glu Glu Thr Asn Val
 210 215 220
 Asp Asp Gly Asn Glu Ala Ile Thr Arg Leu Ser Glu Lys Pro Val Phe
 225 230 235 240
 Asp Tyr Thr Thr Thr Arg Ser Val Asp Leu Glu Cys Ser Ile Thr Gly
 245 250 255
 Met Ile Pro Pro Ser Ser Ile Thr Arg Lys Ile Ala Glu Trp Val Tyr
 260 265 270
 Ala Asn Phe Ser Asn Val Glu Glu Lys Ser Lys Arg Asn Val Glu Leu
 275 280 285
 Glu Leu Lys Phe Gly Lys Ile Ile Asp Lys Arg Ser Gly Asn Arg Ile
 290 295 300

Asp Leu Asn Val Val Thr Glu Cys Ile Phe Thr Asp His Ser Ser Val
 305 310 315 320
 Phe Phe Asp Met Gln Val Glu Glu Val Ala Trp Lys Glu Ile Thr Lys
 325 330 335
 Phe Leu Asp Glu Leu Glu Lys Ser Phe Gln Glu Gly Lys Lys Gly Arg
 340 345 350
 Lys Phe Lys Thr Leu Glu Ser Asp Asn Thr Asp Ser Phe Tyr Gln Leu
 355 360 365
 Gly Arg Lys Gly Glu His Pro Lys Arg Ile Arg Val Thr Lys Asp Asn
 370 375 380
 Leu Leu Ser Pro Pro Arg Leu Val Ala Ile Gln Lys Glu Arg Val Ala
 385 390 395 400
 Asp Leu Tyr Ile His Asn Pro Gly Ser Leu Phe Asp Leu Arg Leu Ser
 405 410 415
 Met Ser Leu Glu Ile Pro Val Pro Gln Gly Asn Ile Glu Ser Ile Ile
 420 425 430
 Thr Lys Asn Lys Pro Glu Met Val Arg Glu Lys Lys Arg Ile Ser Tyr
 435 440 445
 Thr His Pro Pro Thr Ile Thr Lys Phe Asp Leu Thr Arg Val Ile Gly
 450 455 460
 Asn Lys Thr Glu Asp Lys Tyr Glu Val Glu Leu Glu Ala Gly Val Met
 465 470 475 480
 Glu Ile Phe Ala Ala Ile Asp Lys Ile Gln Lys Gly Val Asp Asn Leu
 485 490 495
 Arg Leu Glu Glu Leu Ile Glu Val Phe Leu Asn Asn Ala Arg Thr Leu
 500 505 510
 Asn Asn Arg Leu Asn Lys Ile Cys
 515 520

<210> 122

<211> 198

<212> PRT

<213> Candida albicans

<400> 122

Met Val Asn Gly Pro Ala Glu Leu Arg Arg Lys Leu Val Ile Val Gly
 1 5 10 15
 Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile Val Phe Ser Lys Gly
 20 25 30
 Thr Phe Pro Glu Val Tyr Val Pro Thr Val Phe Glu Asn Tyr Val Ala
 35 40 45
 Asp Val Glu Val Asp Gly Arg Lys Val Glu Leu Ala Leu Trp Asp Thr
 50 55 60
 Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro Leu Ser Tyr Pro Asp
 65 70 75 80
 Ser Asn Val Ile Leu Ile Cys Phe Ser Val Asp Ser Pro Asp Ser Leu
 85 90 95
 Asp Asn Val Leu Glu Lys Trp Ile Ser Glu Val Leu His Phe Cys Gln
 100 105 110
 Gly Val Pro Ile Ile Leu Val Gly Cys Lys Ser Asp Leu Arg Asp Asp
 115 120 125
 Pro His Thr Ile Glu Ala Leu Arg Gln Gln Gln Gln Gln Pro Val Ser
 130 135 140
 Thr Ser Glu Gly Gln Gln Val Ala Gln Arg Ile Gly Ala Ala Asp Tyr
 145 150 155 160
 Leu Glu Cys Ser Ala Lys Thr Gly Arg Gly Val Arg Glu Val Phe Glu
 165 170 175

Ala Ala Thr Arg Ala Ser Leu Arg Val Lys Glu Lys Lys Glu Lys Lys
 180 185 190
 Lys Lys Cys Val Val Leu
 195

<210> 123

<211> 708

<212> PRT

<213> Candida albicans

<400> 123

Met Glu Val Thr Ser Leu Pro Ile Lys Leu Gln Pro Ser Asn Ile Arg
 1 5 10 15
 Pro Ile Ala Phe Arg Ile Leu Ser Lys Lys His Gly Leu Asn Ile Asn
 20 25 30
 Thr Asp Ala Leu Ala Ile Leu Thr Glu Thr Ile Gly Tyr Lys Phe Gly
 35 40 45
 Thr Asp Trp Lys Ser Val Arg Ser Gln Gln Phe Leu Glu Glu Val Ala
 50 55 60
 Lys Val Trp Lys Ile Glu Asp Arg Gly Leu Phe Ile Asp Gly Asp Gly
 65 70 75 80
 Leu Lys Gln Val Leu Lys Asp Met Asn Ser Lys Ser Ser Asn Asp Thr
 85 90 95
 Lys Arg Ala His Arg Thr Asp Thr Leu Val Asp Ile Thr Asn Asp Gly
 100 105 110
 Asn Gln Asn His Thr His Ser His Gln Asp Lys Gln Ile Ser Phe Glu
 115 120 125
 Asp Lys Asn Met Glu His Glu Glu Arg Asp Asp Val Pro Ile Asn Trp
 130 135 140
 Gln Asp Tyr Phe Lys Val Val Ser Pro Asn Asn Gln Pro Thr Ser Ile
 145 150 155 160
 Phe Asp Lys Thr Arg Lys Gln Phe Asp Ile Val Phe Lys Asn Asn Asp
 165 170 175
 Asp Lys Asp Lys Lys Ala Glu Arg Gly Gly Lys Leu Glu Ser Ile Val
 180 185 190
 Ala Glu Leu Val Lys Asn Leu Pro Ala Ser Ile Glu Ser Phe Asn Asn
 195 200 205
 Arg Tyr Tyr Leu Leu Ser Asp Arg Leu Ser Arg Asn Glu Asn Phe Gln
 210 215 220
 Lys Lys Ser Leu Ile Ser Leu Ser Ala Leu Asn Ser Phe Lys Glu Gly
 225 230 235 240
 Lys Thr Asp Ser Ile Thr Gly His Glu Ile Ser Leu Ile Lys Asn Met
 245 250 255
 Leu Gly Arg Asp Gly Gln Lys Phe Leu Ile Phe Gly Leu Leu Ser Lys
 260 265 270
 Asn Ala Asn Asp Glu Tyr Thr Leu Glu Asp Glu Thr Asp His Ile Glu
 275 280 285
 Leu Asn Leu Ser Gln Ala Phe Lys Ser Gln Gly Leu Phe Tyr Cys Pro
 290 295 300
 Gly Met Phe Leu Leu Val Glu Gly Ile Tyr Ser Ala Ser Gly Gly Asn
 305 310 315 320
 Ser Asn Gln Asp His Gly Tyr Ile Gly Gly Cys Phe Tyr Val Ser Asn
 325 330 335
 Ile Gly His Pro Pro Ser Glu Arg Arg Glu Thr Ser Leu Asp Val Tyr
 340 345 350
 Gly Asn Leu Asp Phe Leu Gly Met His Arg Gln Ile Ala Pro Val Thr
 355 360 365

Gly Glu Lys Ile Thr Lys Ile Ser Lys Lys Phe Lys Lys Arg Leu Val
 370 375 380
 Leu Ile Glu Lys Thr Leu Tyr Asn His Lys Leu Ile Phe Val Gly Thr
 385 390 395 400
 Asp Leu Tyr Leu Asp Phe Lys Val Leu Asp Gly Leu Arg Lys Phe
 405 410 415
 Phe Gln Lys Leu Glu Asn Ser Ile Ile Glu Ser Ile Glu Asp Glu Glu
 420 425 430
 Gly Gln Met Ala Glu Gly Thr Asn Ile Pro Leu Ala Leu Val Phe Thr
 435 440 445
 Gly Ser Phe Val Ser Lys Pro Leu Ser Val Thr Asn Ser Ser Val Thr
 450 455 460
 Asn Ile Thr Asn Ser Glu Ser Tyr Lys Ser Asn Phe Asp Asn Phe Thr
 465 470 475 480
 Thr Ile Val Ser Lys Tyr Pro Asn Ile Val Ser Arg Cys Lys Ile Ile
 485 490 495
 Leu Ile Pro Gly Lys Asn Asp Pro Trp Gln Ser Thr Tyr Ser Leu Gly
 500 505 510
 Ser Ser Ser Leu Asn Tyr Phe Pro Gln Ser Ser Ile Pro Lys Val Phe
 515 520 525
 Ile Asn Arg Leu Glu Lys Leu Leu Pro Lys Gly Asn Leu Val Val Ser
 530 535 540
 Trp Asn Pro Thr Arg Ile Asn Tyr Leu Ser Gln Glu Leu Val Val Phe
 545 550 555 560
 Lys Asp Glu Leu Met Thr Lys Leu Lys Arg Asn Asp Ile Ile Phe Pro
 565 570 575
 Arg Asp Ile Gln Glu Gln Glu Glu Leu Ile Ala Gln Asp Asp Gln Arg
 580 585 590
 Thr Asn Glu Glu Arg Ile Asn Asn Leu Ile Gln Asn Lys Asn Thr His
 595 600 605
 Leu Pro Ser Lys Ile Lys Gln Ala Arg Lys Leu Val Lys Thr Ile Leu
 610 615 620
 Asp Gln Gly Asn Leu Gln Pro Phe Leu Lys Asn Leu Lys Leu Ile Asn
 625 630 635 640
 Leu Ala Tyr Asp Tyr Ser Leu Arg Ile Glu Pro Leu Pro Ser Val Ile
 645 650 655
 Ile Leu Asn Asp Ser Ser Phe Asp Asn Phe Glu Val Thr Tyr Asn Gly
 660 665 670
 Cys Lys Val Val Asn Ile Thr Ser Val Val Ser Leu Asn Asn Arg Lys
 675 680 685
 Phe Asn Tyr Val Glu Tyr Tyr Pro Gly Thr Lys Arg Phe Glu Phe Lys
 690 695 700
 Asp Leu Tyr Phe
 705

<210> 124

<211> 86

<212> DNA

<213> Artificial Sequence

<220>

<223> DNA primer

<400> 124

ctctcttttta tattctcgtc aataaaatcg ctcaactcgaa aaccctaataaa aaaagcagac
 aaccccgcgtc tagaactagt ggatcc

60

86

<210> 125

<211> 83
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> DNA primer

<400> 125
 agaaaaaaaa gtaaccacac atgagatgaa ctaaaccaac atcaatcaac cattacacac 60
 caatccgctc tagaactagt gga 83

<210> 126
 <211> 83
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> DNA primer

<400> 126
 ttctatTTTT cagattgact atcctttaac cttctaataca ttacatctt caagaactaa 60
 gttcccgctc tagaactagt gga 83

<210> 127
 <211> 83
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> DNA primer

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 gaggtcgacg gtatcg 76

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 gaggtcgacg gtatcg 76

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agtatccctc gaggtcgacg gtatcg

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A61K 39/00, C07K 16/14, G01N 33/50Street, Montreal, Quebec H3W 2E6 (CA). BOONE,
Charles [CA/CA]; 254 Glenrose Avenue, Toronto, On-
tario M4T 1K9 (CA). BUSSEY, Howard [CA/CA]; 325
Victoria Avenue, Westmount, Quebec H3Z 2N1 (CA).

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(74) Agents: CORUZZI, Laura, A. et al.; Pennie & Edmonds
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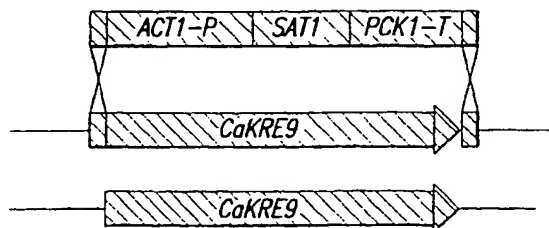
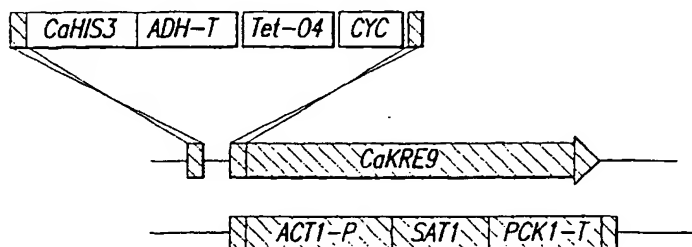
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(75) Inventors/Applicants (*for US only*): ROEMER, Terry
[CA/CA]; 4935 Connaught Avenue, Montreal, Quebec
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[Continued on next page]

(54) Title: GENE DISRUPTION METHODOLOGIES IN FUNGI FOR DRUG TARGET DISCOVERY

• STEP 1: GENE REPLACEMENT

• STEP 2: CONDITIONAL EXPRESSION
BY PROMOTER REPLACEMENT

(57) Abstract: The present invention provides methods and compositions that enable the experimental determination as to whether any gene in the genome of a diploid pathogenic organism is essential, and whether it is required for virulence or pathogenicity. The methods involve the construction of genetic mutants in which one allele of a specific gene is inactivated while the other allele of the gene is placed under conditional expression. The identification of essential genes and those genes critical to the development of virulent infections, provides a basis for the development of screens for new drugs against such pathogenic organisms. The present invention further provides *Candida albicans* genes that are demonstrated to be essential and are potential targets for drug screening. The nucleotide sequence of the target genes can be used for various drug discovery purposes, such as expression of the recombinant protein, hybridization assay and construction of nucleic acid arrays. The uses of proteins encoded by the essential genes, and genetically engineered cells comprising modified alleles of essential genes in various screening methods are also encompassed by the invention.

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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International Application No

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	C07K14/40	C12P21/00	A61K39/00	C07K16/14	G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>WO 00 53781 A (MITOTIX INC (US)) 14 September 2000 (2000-09-14)</p> <p>page 2, line 5 -page 6, line 22 page 13, line 30 -page 17, line 26 page 18, line 5 -page 20, line 10 example 2</p> <p>---</p> <p>-/--</p>	<p>1-6, 8-10,12, 13, 24-26, 28-31</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

25 October 2001

Date of mailing of the international search report

13.2.02

Name and mailing address of the ISA

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De Kok, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/05551

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MENDOZA A ET AL: "Translation elongation factor 2 is encoded by a single essential gene in Candida albicans" GENE, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, NL, vol. 229, no. 1-2, 18 March 1999 (1999-03-18), pages 183-191, XP004161173 ISSN: 0378-1119 cited in the application page 183, column 2, last paragraph -page 184, column 1, paragraph 1 page 188, column 1; figures 1,5 ---</p>	<p>1-6, 8-10,12, 13, 24-26, 28-31</p>
X	<p>WO 97 16540 A (CHEMGENICS PHARMACEUTICALS INC) 9 May 1997 (1997-05-09) page 6, line 5 - line 16 page 7, line 7 - line 18 page 21, line 11 -page 22, line 9 page 27, line 17 -page 30, line 2; figures 4,7 ---</p>	<p>1-6, 8-10,12, 13, 24-26, 28-31</p>
X	<p>MIO TOSHIYUKI ET AL: "Isolation of the Candida albicans homologs of Saccharomyces cerevisiae KRE6 and SKN1: Expression and physiological function" JOURNAL OF BACTERIOLOGY, WASHINGTON, DC, US, vol. 179, no. 7, 1997, pages 2363-2372, XP002156281 ISSN: 0021-9193 cited in the application abstract page 2367, column 1 page 2369, column 2, last paragraph -page 2370, column 1; figure 8 ---</p>	<p>1-6, 8-10,12, 13, 24-26, 28-31</p>
Y	<p>GOW N A R ET AL: "GENES ASSOCIATED WITH DIMORPHISM AND VIRULENCE OF CANDIDA ALBICANS" CANADIAN JOURNAL OF BOTANY, NATIONAL RESEARCH COUNCIL, OTTAWA, CA, vol. 73, no. SUPPL 1, 1995, pages S335-S342, XP000926595 ISSN: 0008-4026 abstract page S336, column 2 page S340, column 1 -page S341, column 1 ---</p>	<p>1</p>
	<p>---</p>	

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/05551

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GARI ELOI ET AL: "A set of vectors with a tetracycline-regulatable promoter system for modulated gene expression in <i>Saccharomyces cerevisiae</i> " YEAST, CHICHESTER, SUSSEX, GB, vol. 13, no. 9, 1997, pages 837-848, XP000926574 ISSN: 0749-503X cited in the application page 838, column 1 page 846, column 2, last paragraph -page 847, column 1, paragraph 2	1
A	---	7,11
A	MIO ET AL: "Cloning of the <i>Candida albicans</i> homolog of <i>Saccharomyces cerevisiae</i> GSC1/ FKS1 and its involvement in beta-1,3-glucan synthesis" JOURNAL OF BACTERIOLOGY, WASHINGTON, DC, US, vol. 179, no. 13, July 1997 (1997-07), pages 4096-4105, XP002115088 ISSN: 0021-9193 cited in the application page 4096, column 2, last paragraph page 4102, column 2, line 6 - line 10	1
A	---	1
A	WO 99 31269 A (UNIV MCGILL (CA)) 24 June 1999 (1999-06-24) page 3, line 22 -page 6, line 7 page 12, line 16 -page 15, line 12	1
A	---	1,27
A	MAO YUXIN ET AL: "Overexpression of a dominant-negative allele of SEC4 inhibits growth and protein secretion in <i>Candida albicans</i> ." JOURNAL OF BACTERIOLOGY, vol. 181, no. 23, December 1999 (1999-12), pages 7235-7242, XP002180711 ISSN: 0021-9193 cited in the application page 7235, column 1, last paragraph page 7235, column 2, last paragraph -page 7236; figure 1 page 7239, column 2, paragraph 2 -page 7240, column 2, paragraph 1 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/05551

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 14-21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-21, 24-31

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 14-21

Present claims 14-21 relate to a collection of diploid fungal strains defined by reference to a desirable characteristic or property, namely comprising strains representing modified alleles of all the different genes in the genome of the fungus.

The claims cover all collections of all diploid fungi having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for NONE of such collections. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the collection by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, NO search has been carried out for those claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-21, 24-31

Invention 1:

A method for constructing a strain of diploid fungal cells and its use for the identification of essential genes

2. Claims: 22, 23 and 32-75 all partially

Invention 2:

A purified or isolated nucleic acid molecule encoding a gene product required for proliferation of *Candida albicans*, wherein said gene product comprises an amino acid sequence of SEQ.ID.No.63; vectors and hosts comprising said nucleic acid; a purified polypeptide comprising an amino acid sequence of SEQ.ID.No.63; a process for producing said polypeptide and uses of said nucleic acid and said polypeptide.

Inventions 3-63:

As invention 2, but limited to each single nucleic acid encoding a gene product having an amino acid sequence in the order listed in claim 32, starting with SEQ.ID.No.64 and ending with SEQ.ID.No.123

For the sake of conciseness, the subject-matter of invention 2 is explicitly defined, the subject-matter of inventions 3-63 is defined by analogy thereto.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/05551

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			WO	0053781 A1	14-09-2000

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